Continuous Glucose Monitoring for Screening for Diabetes in Pregnancy: A comparative effectiveness randomized control trial (PRECISE)

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Continuous Glucose Monitoring for Screening for Diabetes in Pregnancy: A comparative effectiveness randomized control trial (PRECISE)

Study Protocol

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STUDY PROTOCOL

1. BACKGROUND

Gestational diabetes (GDM) is a condition in which carbohydrate intolerance develops during pregnancy. It remains one of pregnancy's most common medical complications, afflicting approximately 10% of all pregnancies in the United States (1). GDM is associated with maternal and fetal complications such as hypertensive disorders of pregnancy, birth injury, fetal macrosomia, cesarean section, neonatal complications, and increased risk of developing diabetes later in life (2). In addition, the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study found that maternal hyperglycemia is associated with adverse perinatal outcomes of increased birth weight and neonatal hyperinsulinemia (3, 4). Timely diagnosis and treatment of GDM improves both maternal and fetal outcomes (5, 6).

To avert the multitude of the complications associated with GDM, universal screening is recommended at 24-28 weeks gestation (5, 7). Currently, screening and diagnosis of GDM can be made through various glucose challenge tests (8). Table 1 lists the current recommendations by various policy for GDM screening (7, 9, 10).

Table 1: GDM Screening Recommendations

Organization (Year)	Test	Criteria for GDM diagnosis
American Diabetes Association (2020)	Universal screening *One Step* 2h PG (75 g OGTT) Or *Two Step* 1h GCT (50g OGCT)/3h OGTT (100g)	FPG ≥ 92 mg/dL 1h PG≥ 180 mg/dL 2h PG ≥ 153 mg/dL Or 1h ≥ 135 or 140mg/dL Fasting ≥ 95 or 105 mg/dL 1hr ≥ 180 or 190 mg/dL 2hr ≥ 155 or 165 mg/dL 3hr ≥ 140 or 145 mg/dL

American College of Obstetrics & Gynecology (2018)	Universal screening *Two-Step* 1h PG (50 g OGCT) 3hr (100g OGTT)	As above
National Institute for Health & Care Excellence (2015)	Targeted high-risk screening *One step* 2h PG (75 g OGTT)	FPG ≥ 100mg/dL 2hr PG ≥ 140 mg/dL
WHO & FIGO (2013)	Universal screening *One step* 2h PG (75g OGTT)	FPG ≥126 mg/dL 2 h PG≥200 mg/dL
International Association of the Diabetes and Pregnancy Study Group (2010	Universal screening *One step* 2h PG (75g OGTT)	FPG ≥ 92 mg/dL 1h PG≥ 180 mg/dL 2h PG ≥ 153 mg/dL

Most institutions follow the American College of Obstetrics & Gynecology (ACOG) recommendations of a two-step assessment during 24 to 28 weeks gestation (2). However, there are at least four limitations of the 50g oral glucose tolerance test (GCT) diagnostic values. First, the one-hour GCT was validated to determine the risk of developing Type II diabetes later in life; the diagnostic cut-off, however, is not centered on preventing adverse maternal or fetal outcomes. Second, a positive one-hour GCT result requires pregnant people to return to the clinic while fasting to complete a three-hour glucose challenge test (GCT). Third, the predictive value changes in different ethnicities due to the varying prevalence of GDM (11). Fourth, there is no available screening test for people who present late to care or those who cannot tolerate the GCT (such as people after bariatric surgery or with significant nausea and vomiting). For those patients the most common management would be to panel their blood sugars for at least 1 week.

Screening in pregnant population

Other traditional diagnostic laboratory values, such as hemoglobin A1c and fasting blood glucose, used in non-pregnant states, have not been reliable or validated during pregnancy. HemoglobinA1c has poor sensitivity and specificity in the diagnosis of GDM, allowing for a high false-negative rate (12). Fasting blood glucose (FBG) was widely studied to decrease the burden associated with GTT, as it is associated with less cost and causes minor discomfort. However, no standardized criteria have been shown to provide reproducible GDM diagnosis (11).

Despite the high prevalence of GDM and complications, very few randomized trials studying the optimal screening test have been conducted (13). A recent randomized trial comparing the single step to the two-step diagnosis showed no difference in perinatal outcomes (14). A Cochrane review in 2015 cited that six small randomized control trials have been completed that have assessed optimal GDM screening. Of the six, only two studies compared the differences between recommended diagnostic tests (7). The findings are listed below.

Table 2: Randomized trials on screening for GDM

Title	RCT	N	Findings
Hillier et al/2020 (14)	RCT: 75g GTT v. 50g GCT/ 100g GTT	23,792	No difference in the primary outcome of a diagnosis of GDM, LGA, CD, HDP, or perinatal composite
Olarinoye et al./2004 (12)	RCT: 75g GTT v. 100g GTT	248	Higher prevalence of GDM in 75g GTT group, No difference in macrosomia or FBG
Shirazian et al/2008 (15)	WHO 75g GTT v. ADA 75g GTT	670	No difference in diagnosis of GDM, CD, macrosomia, instrumental birth

In the U.S., trends of obesity, sedentary lifestyle, cardiovascular disease, and many other risk factors that place patients at high risk of developing GDM are continuing to soar (16). However, with the adverse outcomes associated with GDM for both mother and infant, there is an urgent need to develop a comprehensive and standardized form of screening and diagnosis.

Continuous Glucose Monitoring in pregnancy

Continuous glucose monitoring systems putatively measure interstitial glucose values throughout the day, providing measurements every five minutes wirelessly. Providers are given many glucose values, including the mean, fasting, and range of glucose levels. Unlike a point of care value such as FBG or GTT result, CGM allows for much greater surveillance and detection of hyperglycemic episodes (9). Target values can be programmed into the receiver or mobile app, allowing for calculating time in range.

Prospective studies evaluating the accuracy of CGM during GTT assessed the efficacy of CGM to detect hyperglycemic excursions (17). In addition, CGM has been studied in high-risk patient groups to identify hyperglycemic episodes. CGM has detected abnormal glucose profiles and provided caregivers specific glycemic trends in multiple populations at risk for abnormal glycemic trends, such as morbid obesity, critically ill, polycystic ovarian syndrome (9).

Current two-step testing has many limitations, such as requiring a second diagnostic test that requires specific timing and prolonged laboratory stay (4 hours) with further delaying treatment and diagnosis. Unfortunately, no current

data uses CGM as a screening tool for GDM. CGM is a promising, minimally invasive modality that will provide a more comprehensive evaluation of the glycemic profile of people. Thus, allowing a prompt diagnosis and treatment tailored to each person's glycemic discrepancies recorded by the CGM.

2. RATIONALE FOR A CLINICAL TRIAL

There are multiple reasons for a clinical trial comparing the traditional method of screening for GDM versus

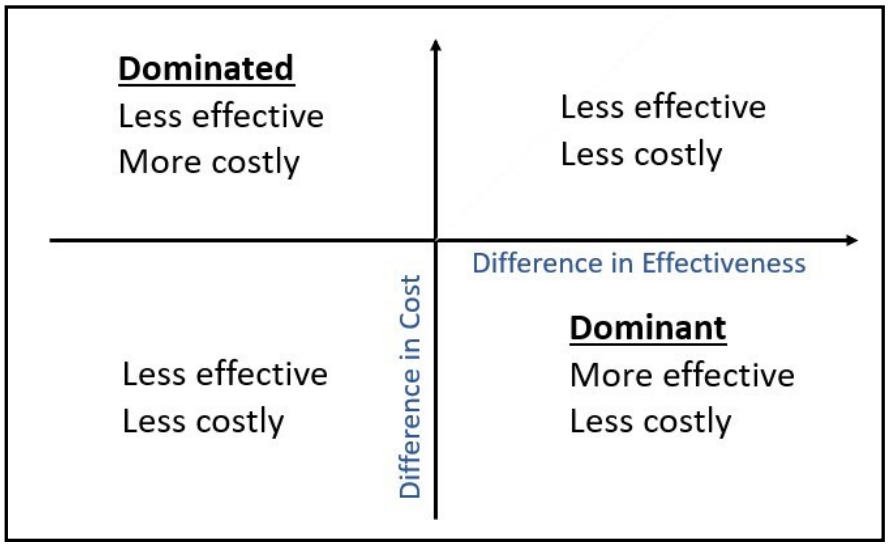
- Need for a diagnostic test that is based on maternal and neonatal outcomes.
- No current consensus on the best screening test for GDM during pregnancy.
- Non-pregnant diagnostic laboratory values, such as Hemoglobin A1c and fasting plasma glucose, do not have reliable diagnostic cut-offs during mid-pregnancy.
- Need for a test that can efficiently diagnose GDM, which does not require additional, lengthy clinic visits.
- The use of CGM permits for a complete glycemic profile as compared to the point of care glucose challenge test, thus allowing for a more specified and thorough treatment of GDM
- Readily available CGM results allow for prompt, individualized treatment.
- There are no current large, ongoing trials studying CGM as a screening tool for GDM.

3. HYPOTHESIS AND OBJECTIVE

3.1 Hypothesis:

We hypothesize that compared to usual care with the two- step screening method, CGM will increase detection of GDM and reduce maternal and neonatal adverse outcomes and health system costs related to GDM. CGM will also be shown to be highly cost-effective in preventing mother-infant dyads from developing maternal or neonatal adverse outcomes. Cost effectiveness may be achieved be either reducing maternal or neonatal health system costs without increasing the rate or heath system costs of adverse maternal or neonatal outcomes. By highly cost effective, we mean that CGM will lie within the dominant quadrant – i.e. the lower right quadrant – of the cost-effectiveness plane (Figure 1).

Figure 1. Cost Effectiveness Plane



3.2 Primary Objectives

The objectives of this randomized controlled trial are:

- To evaluate whether CGM for diagnosis of GDM and improves maternal and neonatal outcomes related to GDM.
- To evaluate whether CGM for GDM diagnosis reduces the health system costs for mother-infant dyads compared to usual care

3.3 PICO Question

Population: Pregnant individuals screening for GDM

Intervention: CGM for GDM screening

Comparison: Usual care with two step GDM screening

Primary Outcome: Composite neonatal outcomes

4. STUDY DESIGN AND POPULATION

4.1 Study Design

This is a single site, multi-clinic randomized controlled trial for pregnant people undergoing gestational diabetes screening in pregnancy.

4.2 Inclusion Criteria

- Maternal age of 18 years or older
- 24-30 weeks gestation undergoing GDM screening

4.3 Exclusion Criteria

- Known diagnosis of Type I and II DM
- History of bariatric surgery
- Multiple gestation pregnancy
- Major fetal anomalies
- Unwilling to use CGM for GDM screening

- Incarcerated subjects
- History of allergic reaction to any of CGM metals or adhesives in contact with the skin
- People with incompatible cellular devices with G6PRO application

5. METHODS AND ASSESSMENT

5.1 Randomization and blinding

- A non-clinical research team member will create computer-generated random sequences to ensure untampered randomization. A permutated block randomization in a random fashion 1:1 ratio will be employed to prevent imbalance in groups.
- Randomization will be stratified by BMI ≥ 40 and clinic site at randomization
- **Blinding:** The research team collecting data will be blinded to group allocation. We will not be able to blind the treating physician or patient to the CGM due to the nature of the intervention.

5.2 Setting

Recruitment will occur in outpatient clinic settings:

- University of Texas, Houston (UTH) outpatient clinics:
  - UT physicians' continuity clinic in the Texas Medical Center
  - Women's Health Center, Bellaire
  - Women's Health Center, Memorial City
  - Women's Health Center, Sugarland

5.3 Recruitment

- Flyers and posters will be placed in clinic work rooms, patient rooms and clinic restrooms with recruitment and study procedure information.
- The diabetes care and education specialist (CDCES) or research staff and collaborators will approach eligible individuals during their clinic appointment.
- The research team will introduce continuous glucose monitoring and the G6/G7PRO CGM device per the manufacturer's use instructions.
- Details of the study, risks and benefits of CGM in pregnancy will be discussed in a private room, and the informed consent form will be reviewed. Once all questions are answered and the individual is amenable to participant in the study, she will be asked to sign a consent form. A copy of consents will be given to the individual. In addition, patients will be approached about the study in either English or Spanish by research personnel fluent in the language.

5.4 Intervention and procedures

- After informed consent is completed; participants will be randomized into either one-hour GCT or CGM screening.
    - Group I will be comprised of one-hour 50g glucose challenge participants for diagnosis of GDM.
    - Group 2 will be participants that have CGM placement for diagnosis.
- CGM will consist of using the Dexcom G6 Pro device (Figure 2). The device will be applied by a trained health care professional in the clinic.
- The system will be set up according to the manufacturer's use instructions.
- The device will be placed on the abdomen or the arm.

- The sensor will stay in place for a maximum of 7 days as recommended by the manufacturer.
- In the event, CGM sensor malfunctions and values of at least three days are not available on Dexcom portal, sensor will be replaced.
- Sensors will not be reused for other patients.
- CGM will be placed for all study participants.
- Group I participants, CGM will be blinded and diagnosis will be based on 1-hour glucose challenge test results as below.
    - 1-hour result ≤ 130 mg/dL, the participant will have passed the challenge test.
    - 1-hour result ≥ 130 mg/dL will complete a three-hour 100g glucose tolerance test. If two out of three values are elevated per Carpenter Coustan criteria (Table 3), the participant will be diagnosed with GDM and treated according to the standard of care.
- Group 1 participants' CGM data will not be observed until completion of study and will not be available to provider.
- Group 1 participants will return transmitter at follow up visit after completion of 7 days. If unable to bring to clinic visit, a prepaid postage will be provided to the participant to return the transmitter.

Figure 2: Dexcom G6 Pro device

- **Group 2** will use CGM for screening for diabetes.
- The Dexcom G6/G7 Pro App will be downloaded on the patient's phone
- A patient profile will be created on the Dexcom Clarity portal
- The patient will receive an email to link their portal to the clinic's portal
- If the patient's phone is not compatible with G6 Pro mobile app, the data will be blinded for her and the provider until the return of the device. Pick-up or mailing of the device will be planned for seven days after placement.
- The patient will receive a message through Epic EMR to remove the CGM one week after placement
- Group 2 will have the device in place for a total of 7 days and reviewed by the Diabetes team after 7-10 days after CGM placement. The recommended range for glucose during pregnancy is defined as 63-140 mg/dL (18). The time above range has been defined as ≥ 140 mg/dL, greater than 10% of total CGM

placement time. Based on the results of our prospective observational study of blinded CGM placement at time of one-hour GCT of pregnant people ≤ 30 weeks a CGM metric of time above range ≥ 10% was associated with higher rates of adverse neonatal outcomes.

- The following criteria will currently be used to diagnose gestational diabetes in the CGM group:
    - Time above range (≥140 mg/dL) ≥ 10% of the time while using CGM or
    - Average glucose≥130 mg/dL or
    - Any glucose value ≥200 mg/dL
- Group I will receive routine prenatal care follow-up depending upon one-hour glucose results as written above.
- Group 2 will complete CGM and proceed with treatment if positive screening is found, as written above.
- Management of GDM for both groups would include:
    - Consultation and follow up with Certified Diabetes Care and Education Specialist (CDCES)
    - The patients will be instructed to self-monitoring of blood glucose (SMBG) levels four times a day through a glucometer: fasting, 1-2 hour postprandial as recommended by the ACOG guidelines.
    - Patients will be managed according to the ACOG recommendations of goals (2):
        - Fasting: ≤ 95 mg/dL
        - 1 hour postprandial: ≤ 140 mg/dL

    - 2 hour postprandial: ≤ 120 mg/dL
  - Initiation of medication if consistently elevated blood sugars following diet adjustment per provider discretion
- Participants will be asked to continue to follow up as the standard of care.
- No extra visits will be scheduled
- Both groups will be followed throughout pregnancy, delivery, and postpartum.
- A release of records form will be signed at randomization so that in case the participant delivers at another center; we can still obtain records from the delivery.
- The research team will collect participant data, including demographic characteristics, medical history, obstetric history, labor course, and maternal and neonatal outcomes, by reviewing the electronic medical records and surveying the people during prenatal visits and the 6- week postpartum clinical appointment.
- All participants will receive a $20 gift card after completing the diabetes screening (i.e., 1hGCT/3h OGTT if screened positive/7 days with GCM).
- All participants will receive a $20 gift card following delivery.

6. OUTCOME MEASURES

6.1 Primary outcome:

- Composite Adverse Neonatal Outcome including one or more of the followings: (time frame: from enrollment to discharge)

- Large for gestational age (LGA): weight over 90th percentile of the expected value according to gestational age (using the nomogram by Duryea EL et al). (19)
- Shoulder dystocia: defined as the need for any extra maneuvers, other than gentle downward traction of the fetal head to deliver the fetal body after the fetal head has been delivered
- Birth injury: skull, clavicular, humerus fracture, or brachial plexus injury
- Neonatal hypoglycemia defined as requiring intravenous or oral glucose
- Respiratory distress: the need for at least 4 hours of respiratory support with supplemental oxygen, continuous positive airway pressure, or ventilation at the first 24 hours of life
- Fetal or neonatal death (within 28 days of birth)

6.2 Secondary outcomes

Maternal-

- Feasibility of CGM use for GDM screening
- Diabetic medication: use of any glycemic control agent during pregnancy or 6- week postpartum period.
- Polyhydramnios during pregnancy not related to known fetal anomaly
- Ultrasound diagnosis of estimated fetal weight >90%ile in the third trimester based on the (using the nomogram published by Duryea EL et al) (19)
- Preterm birth: delivery less than 37 weeks of gestation

- Induction of labor
- Pregnancy-induced hypertension: gestational hypertension, preeclampsia with or without severe features, HELLP syndrome, or eclampsia per ACOG guidelines.
    - Gestational hypertension: new-onset hypertension (systolic ≥ 140 mm Hg or diastolic ≥ 90 mm Hg) without proteinuria
    - Preeclampsia: hypertension (systolic ≥ 140 mm Hg or diastolic ≥ 90 mm Hg) with proteinuria or serum laboratory abnormalities (platelets ≤ 100,000, serum aspartate aminotransferase ≥ 80 IU/mL, creatinine ≥ 1.2 mg/dL. They are classified as with or without severe features.
        - Severe features: systolic ≥ 160 mm Hg, diastolic ≥ 110 mm Hg, persistent headache, pulmonary edema, or any serum laboratory abnormalities as above
        - Proteinuria: protein excretion exceeding 300mg in 24 hours, a protein: creatinine ratio of ≥ 0.3 or 1+ proteinuria or greater on urine dipstick
        - HELLP Syndrome: hemolysis (serum bilirubin ≥ 1.2, low serum haptoglobin ≤ 25, lactate dehydrogenase (LDH) > 2 times upper limit of normal based on laboratory-specific reference ranges or severe anemia unrelated to blood loss), elevated liver enzymes (aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 times the upper limit

of normal based on laboratory-specific reference ranges) and low platelet count (≤ 100,000)

- Eclampsia: seizures

- Admission for poor glucose control
- Primary cesarean section
- Postpartum hemorrhage: defined as ≥ 1000ml or need for blood transfusion
- Endometritis
- Wound complications
- Diagnosis of type 2 diabetes during postpartum (according to the 1h 75g GTT)

Neonatal:

- Large for gestational age (LGA): weight over 90th percentile of the expected value according to gestational age (using the nomogram by Duryea EL et al). (19)
- Shoulder dystocia: defined as the need for any extra maneuvers, other than gentle downward traction of the fetal head to deliver the fetal body after the fetal head has been delivered
- Birth injury: skull, clavicular, humerus fracture, or brachial plexus injury
- Neonatal hypoglycemia defined as requiring intravenous or oral glucose
- Respiratory distress: the need for at least 4 hours of respiratory support with supplemental oxygen, continuous positive airway pressure, or ventilation at the first 24 hours of life

- Fetal or neonatal death (within 28 days of birth)
- Apgar score < 7 at 5 min
- Neonatal intensive care unit (NICU) admission
- NICU length of stay
- Neonatal hypoglycemia: ≤40 mg/dL in the first 24 hours of life and less than 50 mg/dL after or requiring medical therapy
- Neonatal polycythemia defined as hematocrit (Hct) or hemoglobin (Hgb) level above the upper limit of normal (>2 standard deviations) for gestational and postnatal age.
- Neonatal hyperbilirubinemia requiring phototherapy
- Maximum bilirubin level
- Umbilical cord pH (arterial and venous)
- Need for intravenous glucose therapy
- Small for gestational age, defined as a weight below 10th percentile of the expected value according to gestational age (using the nomogram published by Duryea EL et al) (19)

<u>Mother-Infant Dyad</u>

- Total health system costs for mothers and infants
- Cost-effectiveness of CGM relative to usual care, assessed as the total incremental maternal and neonatal health system costs (savings) per prevented mother-infant dyad from developing a maternal adverse outcome (preterm birth, induction of labor, pregnancy-induced hypertension, admission for poor glucose control, primary cesarean section, postpartum hemorrhage,

endometritis or wound complications) or a neonatal adverse outcome (LGA, shoulder dystocia, birth injury, neonatal hypoglycemia, respiratory distress, fetal or neonatal death within 28 days of birth).

Costs will be assessed from the health system perspective based on the total costs for all the services provided to both the participating women and their neonates from randomization through either 6-weeks postpartum or discharge home (whichever is later). Hospital costs incurred within the Memorial Hermann Hospital System (MHHS) will be obtained from claims data and will be based on hospital-specific costs as assigned in the cost-accounting system for each of the 14 hospitals of the MHHS. Hospital costs incurred at hospitals outside of MHHS will be estimated based on mean costs of these encounters at MHHS. Costs for inpatient and outpatient services provided by the UTH physicians will be estimated based on UTH claims data and Relative Value Units (RVUs) from the Medicare Fee Schedule. The costs for the intervention group will be augmented by the acquisition costs of the Dexcom G6 Pro device, which will be based on the average wholesale price as listed in the Micromedex Redbook. All costs will be inflated to the year of analysis based on the Consumer Price Index for medical services.

7. SAMPLE SIZE AND STATISTICAL METHODS

7.1 Determination of Sample Size

As stated above, based on the results of our prospective observational study of blinded CGM placement at time of one-hour GCT of pregnant people ≤ 30 weeks

gestation we would like to adjust the sample size for this trial. A CGM metric of time above range ≥ 10% was associated with higher rates of adverse neonatal outcomes of preterm birth, intravenous glucose therapy and longer hospitalization. The findings of this study serves as the basis of diagnosis of GDM through CGM for our trial. Based on the results of this prospective trial the estimated rate of the primary outcome was 40%. In this trial we would include a more diverse population with a lower rate of factors associated with GDM such as lower BMI, different race and ethnicity. Our assumption is that the rate of the primary outcome will be 25%.

Sample size calculations using a Bayesian analysis with different probability thresholds are presented in Table 4. In order to detect a 30% reduction in the rate of adverse neonatal outcome between the control and intervention with 90% power and a Bayesian posterior probability of 75% (of any reduction), 734 individuals (367 per group) will need to be diagnosed with GDM. With a 10% loss to follow up, 816 people in total will need to be enrolled. A total of 1020 individuals would need to be approached, to accommodate an expected enrollment rate of 80%.

7.2 Statistical and analysis plan

An intention to treat analysis will be conducted. All outcomes will be analyzed using generalized linear models (GLMs) and will include stratifying variables of BMI and clinic site as covariates. Primary outcome and all other binary outcomes will be analyzed with a logistic model. Secondary outcomes will be analyzed using appropriate distributional assumptions, i.e. negative binomial for counts and normal for continuous outcomes. We will report relative risks or group mean differences and 95% confidence intervals (CIs). Differences in costs will be assessed using a generalized linear model (GLM) with log-

link and gamma distribution. We will also compute the incremental cost-effectiveness ratio (ICER) of the total health system costs (savings) per prevented mother-infant dyad from developing an adverse outcome using a joint GLM with log link for costs and probit for maternal or neonatal adverse outcomes. We will induce dependency between costs and the adverse outcomes through shared random effects in the joint model.

Planned Bayesian analysis:

We will also conduct a Bayesian analysis of the primary outcome and of costs and cost-effectiveness. Sample size calculations using a Bayesian analysis with different probability thresholds are presented in Table 4. The composite primary outcome will be evaluated with a Bayesian binomial model. Finally, we conservatively set a neutral prior probability centered at a relative risk (RR) of 1.0 (*i.e.*, a priori no effect on the outcome) and a 95% credible interval of 0.3-3.3 encompassing the largest likely effect size for major outcomes in randomized trials. This neutral prior will also be used to assess cost differences between the two treatment groups. Finally, we will report RR and 95% credible intervals and the probability of reduced adverse neonatal outcomes and costs, as well as the probability that the ICER will fall in the dominant quadrant of the cost-effectiveness plane (Figure 1).

Table 4: Bayesian power to declare efficacy depending on level of evidence (probability threshold)

Control Rate	Treatment Rate	# patients /group	Prob(RR<1) > specified threshold					
			70%	75%	80%	85%	**90%**	**95%**
0.4	0.24	60	0.92	0.89	0.85	0.79	0.71	

0.4	0.28	120	0.93	0.89	0.85	0.82	0.75	
0.4	0.24	110	0.98	0.98	0.96	0.93	**0.90**	
0.4	0.28	210	0.98	0.97	0.96	0.94	**0.90**	
0.35	0.245	236	0.98	0.97	0.95	0.93	**0.89**	**0.80**
0.30	0.21	294	0.98	0.97	0.95	0.93	**0.89**	**0.80**
0.25	0.175	367	0.98	0.97	0.95	0.93	**0.89**	**0.80**
0.20	0.14	484	0.97	0.96	0.95	0.92	**0.88**	**0.80**

Interim analysis after 50% enrollment will be performed to assess the frequency of the primary and secondary outcomes. At that point, a decision will be made to see if there is a need to adjust the sample size.

7.3 Ancillary Studies

1. Satisfaction survey: All participants will be given a short, anonymized survey after completing their screening test. The aim of the survey is to assess participant satisfaction with the screening method they received and care provided throughout study period. The survey will take less than five minutes to complete. The survey will be scored in a Likert-type scale allowing for results to undergo descriptive analysis.

2. Procedure specific satisfaction surveys: We would like to administer a satisfaction survey specific to each screening arm: routine care and CGM placement. Participants will be given a short, anonymized survey after completing their screening test. The aim of the survey is to assess participant's experience, perception and satisfaction with the 2-step glucose tests and CGM application. The surveys will take less than five minutes to complete. The surveys will be scored in a Likert-type scale allowing for results to undergo descriptive analysis.

3. Pre-specified secondary analysis: We have planned for a pre-specified secondary analysis after completion of data analysis. There are as follows:

- Blood sugars using blinded CGM with 1-hour GCT results and composite maternal and adverse outcomes.
- Evaluation of one-hour screening GCT threshold and composite maternal and adverse outcomes.
- Evaluation of one abnormal value during 3-hour GTT and composite maternal and adverse outcomes.
- Risk factors and adverse outcomes associated with ultrasound diagnosed large for gestational age fetus.
- Risk factors and adverse outcomes associated with large for gestational age neonates.
- Fetal growth or amniotic fluid abnormalities during third trimester ultrasound exam among GDM.
- Gestational diabetic outcomes with and without Hypertensive Disorder of Pregnancy.
- Compliant versus non-compliant gestational diabetic: risk factors and associated adverse outcomes.
- The racial and ethnic disparity among gestational diabetics.
- Risk factors associated with neonatal hypoglycemia.
- Evaluation of time above range using CGM and associated neonatal outcomes.

- Maternal hypoglycemia using CGM and composite maternal and adverse outcomes.
- Maternal breastfeeding and diabetes status and associated maternal and neonatal outcomes.
- Maternal breastfeeding, obesity and diabetes status and associated maternal and neonatal outcomes.
- Maternal breastfeeding and CGM glycemic profile and associated maternal and neonatal outcomes.
- Incremental cost for prevention of Type II DM in life using a model method.

7.4 Feasibility

Our clinics see greater than 250 people a week and approximately 6,000 deliveries at our four participating centers. We aim to enroll about ten people per week, based on the previous prospective CGM in pregnancy study. Assuming 10% of people will decline to participate, we will expect to recruit 816 people in 2 years.

8. SAFETY MEASUREMENTS

8.1 Definitions

Serious adverse events will be monitored throughout the study, though not anticipated.

8.2 Procedures for safety monitoring

A review of available experimental and observational literature has shown benefit in outcomes associated with CGM use in pregnant and non-pregnant people with the minimal risk associated with the device (20).

9. ETHICAL CONSIDERATIONS

9.1 Informed consent

All study candidates will be given a full explanation of the study procedure and allowed to read the entire consent form. In addition, they will be given an opportunity to ask any questions. After all, questions have been answered, and the Investigator is confident that the participant understands the requirements of the study, the participant will sign the consent form. In addition, the participant will receive a copy of the informed consent.

9.2 Institutional review board

The Principal Investigator will obtain approval of the research protocol from the IRB. Per U.S. law, the study will be registered in www.clinicaltrials.gov for public access.

9.3 Subject confidentiality

A study number will be assigned to each participant prior to collecting the data. This will maintain the subject's anonymity as they will be de-identified. There will be a record of the participants at the study site to each assigned study number.

The research staff completed the required Collaborative Institution Training Initiative (CITI Training). Access to personal information will be limited to investigators only. Therefore, they are required to keep all information confidential.

In addition, Electronic Medical Record, *Epic,* will be used for pre-screening of individual characteristics. Once identified, participant will be approached via EPIC secured portal messaging system and/or contacted via phone for presentation of research study. If interested, individual will be scheduled a research portal visit.

A secure research portal created by University of Texas, Houston *Epic* Personnel will maintain a screening and actively enrolled participant list. Access will only be granted to those included on the IRB.

The participants will be de-identified when data is reported in any format, including but not limited to medical journals or scientific meetings.

10. DATA HANDLING AND RECORD-KEEPING

10.1 Access to source documents

Research personnel will perform data collection through the abstraction of participant electronic medical records from multiple sites. Demographics, variables, and outcomes will be collected and entered into a Redcap database and the Dexcom data capture platform. Attached to this protocol is a detailed list of variables that will be collected. Data will be obtained from randomization up until 6 weeks postpartum.

10.2 Records Retention:

Data will be collected and de-identified in the UTHealth Redcap system. At the time of study completion, approved protocol and all other supporting documents pertaining to the project will be retained. Data will be de-identified and available for future analysis. Following completion of the study and analysis of data, the de-identified data will be shared to Dexcom Inc.

10.3 Quality control assurance

The Principal Investigator and co-investigators will go through all the files to verify that the data is reliable and complete. Verification will be completed through assessment by Principal Investigator and co-investigator.

11. BUDGET

This study has been awarded the Learning Health Care (LHC) award. LHC is an award granted to University of Texas, Houston faculty that have proposed a study that is a quality improvement project or interventional study that advances patient care and outcomes.

The remainder of funding required for the entirety of this study will be provided by DexCom, Inc., a Delaware corporation located at 6340 Sequence Drive, San Diego, California 92121. Projected study costs are depicted in the attached excel sheet.

References

1. Gestational Diabetes Aug 2021. https://www.cdc.gov/diabetes/basics/gestational.html].
2. ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstet Gynecol. 2018;131(2):e49-e64. doi: 10.1097/AOG.0000000000002501. PubMed PMID: 29370047.
3. Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008;358(19):1991-2002. doi: 10.1056/NEJMoa0707943. PubMed PMID: 18463375.
4. Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med. 2009;361(14):1339-48. doi: 10.1056/NEJMoa0902430. PubMed PMID: 19797280; PubMed Central PMCID: PMC2804874.
5. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS, et al. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med. 2005;352(24):2477-86. Epub 20050612. doi: 10.1056/NEJMoa042973. PubMed PMID: 15951574.
6. Association AD. 14. Management of Diabetes in Pregnancy:. Diabetes Care. 2020;43(Suppl 1):S183-S92. doi: 10.2337/dc20-S014. PubMed PMID: 31862757.
7. Farrar D, Duley L, Medley N, Lawlor DA. Different strategies for diagnosing gestational diabetes to improve maternal and infant health. Cochrane Database Syst Rev. 2015;1:CD007122. Epub 20150121. doi: 10.1002/14651858.CD007122.pub3. PubMed PMID: 25604891.
8. Vandorsten JP, Dodson WC, Espeland MA, Grobman WA, Guise JM, Mercer BM, et al. NIH consensus development conference: diagnosing gestational diabetes mellitus. NIH Consens State Sci Statements. 2013;29(1):1-31. Epub 20130306. PubMed PMID: 23748438.
9. Bhattacharya S, Nagendra L, Krishnamurthy A, Lakhani OJ, Kapoor N, Kalra B, et al. Early Gestational Diabetes Mellitus: Diagnostic Strategies and Clinical Implications. Med Sci (Basel). 2021;9(4). Epub 20210923. doi: 10.3390/medsci9040059. PubMed PMID: 34698239; PubMed Central PMCID: PMC8544345.
10. Moyer VA, Force USPST. Screening for gestational diabetes mellitus: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;160(6):414-20. doi: 10.7326/M13-2905. PubMed PMID: 24424622.
11. Agarwal MM. Gestational diabetes mellitus: Screening with fasting plasma glucose. World J Diabetes. 2016;7(14):279-89. doi: 10.4239/wjd.v7.i14.279. PubMed PMID: 27525055; PubMed Central PMCID: PMC4958688.
12. Rayis DA, Ahmed ABA, Sharif ME, ElSouli A, Adam I. Reliability of glycosylated hemoglobin in the diagnosis of gestational diabetes mellitus. J Clin Lab Anal. 2020;34(10):e23435. Epub 20200702. doi: 10.1002/jcla.23435. PubMed PMID: 32614103; PubMed Central PMCID: PMC7595906.
13. Bulletins—Obstetrics ACoOaGCoP. ACOG Practice Bulletin No. 201: Pregestational Diabetes Mellitus. Obstet Gynecol. 2018;132(6):e228-e48. doi: 10.1097/AOG.0000000000002960. PubMed PMID: 30461693.

14. Hillier TA, Pedula KL, Ogasawara KK, Vesco KK, Oshiro CES, Lubarsky SL, et al. A Pragmatic, Randomized Clinical Trial of Gestational Diabetes Screening. N Engl J Med. 2021;384(10):895-904. doi: 10.1056/NEJMoa2026028. PubMed PMID: 33704936.
15. Shirazian N, Mahboubi M, Emdadi R, Yousefi-Nooraie R, Fazel-Sarjuei Z, Sedighpour N, et al. Comparison of different diagnostic criteria for gestational diabetes mellitus based on the 75-g oral glucose tolerance test: a cohort study. Endocr Pract. 2008;14(3):312-7. doi: 10.4158/EP.14.3.312. PubMed PMID: 18463038.
16. Sagi-Dain L. Obesity in Pregnancy: ACOG Practice Bulletin, Number 230. Obstet Gynecol. 2021;138(3):489. doi: 10.1097/AOG.0000000000004527. PubMed PMID: 34412071.
17. Voormolen DN, DeVries JH, Sanson RME, Heringa MP, de Valk HW, Kok M, et al. Continuous glucose monitoring during diabetic pregnancy (GlucoMOMS): A multicentre randomized controlled trial. Diabetes Obes Metab. 2018;20(8):1894-902. Epub 20180508. doi: 10.1111/dom.13310. PubMed PMID: 29603547.
18. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care. 2019;42(8):1593-603. Epub 20190608. doi: 10.2337/dci19-0028. PubMed PMID: 31177185; PubMed Central PMCID: PMC6973648.
19. Duryea EL, Hawkins JS, McIntire DD, Casey BM, Leveno KJ. A revised birth weight reference for the United States. Obstet Gynecol. 2014;124(1):16-22. Epub 2014/06/06. doi: 10.1097/AOG.0000000000000345. PubMed PMID: 24901276.
20. Soliman A, DeSanctis V, Yassin M, Elalaily R, Eldarsy NE. Continuous glucose monitoring system and new era of early diagnosis of diabetes in high risk groups. Indian J Endocrinol Metab. 2014;18(3):274-82. doi: 10.4103/2230-8210.131130. PubMed PMID: 24944918; PubMed Central PMCID: PMC4056122.
21. Secher AL, Madsen AB, Ringholm L, Barfred C, Stage E, Andersen HU, et al. Patient satisfaction and barriers to initiating real-time continuous glucose monitoring in early pregnancy in women with diabetes. Diabet Med. 2012;29(2):272-7. doi: 10.1111/j.1464-5491.2011.03426.x. PubMed PMID: 21883435.