CAN "CONTINUOUS GLUCOSE MONITORS" (CGMS) IMPROVE POSTPARTUM (PP) GESTATIONAL DIABETES (GDM) SCREENING FOR DIABETES? THE PPCGMS INTERVENTION AFTER GDM TRIAL

INVESTIGATOR-INITIATED STUDY PROPOSAL

Principal Investigator: Karen Elkind-Hirsch, MSc., PHD

Co-Investigator: Edward Veillon Jr. MD
Woman's Research Center
Woman's Maternal Fetal Medicine Department
100 Woman's Way
Baton Rouge, LA 70817

Sponsor: Woman's Hospital

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Correspondence to:

Karen Elkind-Hirsch, MSc., PhD
Director of Scientific Research
100 Woman's Way, Baton Rouge, Louisiana 70817
225-231-5278 | Karen.Elkind-Hirsch@womans.org

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Background

Gestational diabetes mellitus (GDM), a complication of glucose intolerance with first recognition in pregnancy, is one of the most common medical problems in pregnancy and strongly linked with the development of type 2 diabetes (T2D) later in life (1–3). Thirty percent of women with GDM will have persistent postpartum dysglycemia, and up to 70% ultimately receive the diagnosis of T2D within 10 years postpartum (4,5). Therefore, postpartum blood glucose screening is important to detect prediabetes and T2D, allowing timely treatment (3-7). For this reason, both the American Diabetes Association (ADA) and American College of Obstetrics & Gynecology (ACOG) recommend a 2-h 75-gram oral glucose tolerance test (OGTT) for all women who had GDM 6–12 weeks after delivery to detect persisting glucose intolerance or diabetes mellitus after pregnancy (8).

Unlike other laboratory tests performed, the OGTT involves several phases, including the need to fast for several hours, to drink a concentrated glucose solution which can induce unpleasant gastrointestinal effects, the collection of three to four blood samples, and the need to remain seated in the laboratory for two to three hours (9). Ingestion of the glucose solution is an important cause of discomfort for patients undergoing an OGTT. Less than half of the women who had GDM comply to the recommendations of postpartum 75-gram OGTT diabetes screening and the majority do not attend any screening for T2D postpartum (10-12). The average compliance rate for postpartum OGTT testing is 35%, largely related to women perceiving the test as inconvenient (13-15). For example, in England, a study which examined postpartum glucose screening rates in women with a history of GDM, using a nationally representative sample from 127 urban and suburban primary care practices, found that just 18.5% of women had glucose screening within six months of birth [16]. Additional studies have identified reasons for non-attendance or non-completion from the perspective of women (17-19); these reasons included: time pressures, lost laboratory forms, not knowing a test was necessary (15,19) feelings of emotional stress while adjusting to a new baby and fear of a T2D diagnosis [(17-19).

The recommended diabetes screening test postpartum is the OGTT, as hemoglobin A1c (HbA1c) is less sensitive to the rapid glycemic variations and

blood volume changes expected after a recent GDM pregnancy. HbA1c reflects average glycemic exposure over the preceding 2–3 months and is commonly used in people with diabetes to monitor long-term (~3 months) glycemic control (20). Even though the HbA1c is faster, easier, and less expensive to administer, it results in false negative findings 60–70% of the time when the OGTT detects diabetes (21,22). While chronic blood glucose concentrations influence HbA1c levels, many other factors can increase or decrease HbA1c as well, which could lead to questionable HbA1c results and poor alignment with the OGTT. HbA1c levels can be affected by genetic, hematologic, and illness-related factors, especially anemia (23).

Interestingly, the ADA has acknowledged that in patients in whom HbA1c is unreliable (especially those with hemoglobinopathies, altered red cell turnover or impaired renal function), the assessment of other indices of chronic glycemia may be advisable, although their relation with average glucose and prognosis remains uncertain (24). HbA1c reflects the glucose concentration during the entire lifespan of the red blood cells but to the largest extent the 6–8 weeks preceding the time of measurement (20). Certain factors, e.g. red blood cell disorders, could potentially bias the measurement of HbA1c and therefore alternative markers could be useful (24, 25). One such marker is fructosamine which relates to average levels of glucose during the preceding 1 to 3 weeks (24,25). Fructosamine may give an earlier indication of poorly controlled glucose compared to HbA1c. It is a simple, robust and inexpensive biomarker that could potentially be a useful tool in large epidemiological and clinical studies either as a stand-alone indicator of hyperglycemia or in combination with glucose and HbA_1 (25). Importantly, fructosamine may be reliably measured irrespective of fasting or non-fasting. Glycated albumin is the percentage of serum albumin to which a glucose molecule has been nonenzymatically attached, while fructosamine refers to all ketoamine linkages resulting from serum protein glycation (26). The term "fructosamine," therefore, typically refers to all ketoamine linkages that result from glycation of serum proteins. In non-pregnant populations, fructosamine has been shown to adequately identify individuals with diabetes, and to improve diabetes detection when used in combination with HbA1c or fasting glucose (27). Glycated serum proteins, such as fructosamine, may avoid issues related to

RBC turnover and provide viable alternatives to HbA1c as a marker of glycemia. In particular, these biomarkers are not based on hemoglobin and hence, do not depend on RBC turnover (26). Since fructosamine reflects the average levels of blood glucose during the former 1 to 3 weeks, fructosamine also mirrors a poorly controlled glucose metabolism better than HbA1c (27). However, some physiological and pathological conditions can significantly influence the metabolism of fructosamine. In brief, all those clinical conditions that affect protein metabolism potentially influence the concentrations of glycated proteins (28). Thus, physiologic or pathologic conditions linked to hypo-proteinemia (i.e., pregnancy or malnutrition) are more likely to affect the concentration of fructosamine. Another disadvantage of fructosamine is that its concentration is considerably influenced by the levels of immunoglobulins, especially IgA, which are present in abnormal concentration in a broad range of clinical conditions.(29).

Among women who experience glucose abnormalities during pregnancy, screening during the postpartum period offers a window of opportunity for early identification of diabetes and prediabetes. The rates of postpartum T2D screening with an OGTT for women with GDM are not optimal given the majority of women with GDM fail to return for postpartum glucose testing. A new device called a continuous glucose monitor or "CGM" is a small disc that is placed on the arm and can be easily placed and removed by the person wearing it. It is worn for 10 days and can stay in place for activities such as sleeping and showering. Over 10 days, over 1000 sugar measurements are taken without the person wearing the device having to do any testing (30). Continuous glucose monitoring (CGM) systems have been recognized as an ideal method of monitoring glycemic control in diabetic patients (30,31). The data of rigorous 24 h glucose profiles from CGM allow the calculation of glycemic variations, detection of asymptomatic hypoglycaemia and accurately depict the characteristics of blood glucose fluctuations (30,31). In the past decade, CGM has been proven to have similar accuracy to self-monitoring of blood glucose (SMBG) and yet provides better therapy optimization and detects trends in glucose values due to higher frequency of testing. Although CGM has been used successfully in T1D and T2D patients (31), the effectiveness of CGM in improving pregnancy outcomes

complicated by GDM is still understudied (32). Current updated evidence suggests that CGM is superior to SMBG among GDM pregnancies in terms of detecting hypoglycemic and hyperglycemic episodes, which might result in an improvement of maternal and fetal outcomes (33). In addition, CGM is effective at capturing gestational glucose profiles and improving treatment effect among pregnant women with GDM (34,35). Further research is needed to explore the clinical utility such screening and predictive values of CGM for glucose impairment after having diabetes during pregnancy. We need to improve diabetes testing after childbirth in women who experienced gestational diabetes. This will allow us to target our efforts to improve the early diagnosis and treatment of diabetes following GDM. No studies conducted to date have not comprehensively examined whether CGM after delivery can be used in women with a recent history to predict their risk of diabetes.

STUDY OBJECTIVE

Given the damaging effect of prolonged undetected hyperglycemia, prevention and early diagnosis of T2D is cost-saving and of public health importance. This research study is being done to assess if using a glucose sensor (also known as a continuous glucose monitor or CGM) after childbirth can help identify women who are at risk of developing diabetes after having diabetes during pregnancy or gestational diabetes. Currently, screening for diabetes after childbirth is performed with an oral glucose tolerance test 4-16 weeks after delivery, but this is burdensome and most patients are non-compliant. This study will use a CGM worn on the skin for 10 days. The data from the sensor will be compared to the standard oral glucose tolerance test as well as a HbA1c and fructosamine test. This is a single site study from patients with recent GDM that attended the diabetes clinic at Woman's Hospital. The research team plans to enroll 50 participants aged 18 years or older into the study. Participation in the study is expected to last up to 10 days during the postpartum interval. Study procedures include; 1) consent and screening; and 2) sensor placement and download after 10 days of wear postpartum during which an OGTT, fructosamine and HbA1c test will be administered.

STUDY PLANS AND PROCEDURES

Participants and Treatment Regimen

This is a prospective observational study of fifty postpartum women with a recent GDM pregnancy. All participants will be requested to return at 4-16 weeks postpartum for a 75 gm 2-hour OGTT as part of standard care after gestational diabetes. Fifty women with a history of GDM will be enrolled to use a blinded continuous glucose monitor (Dexcom G7). All CGM data will be masked and therefore not available to participants, clinicians, or researchers in real time. Participants otherwise will receive standard clinical care. All participants will be recruited from the Woman's Hospital Diabetes Clinic or from the maternal fetal medicine practice referring to the clinic. Those who wish to participate will provide written informed consent. The Woman's Hospital Institutional Review Board (WHIRB) will have approved both the protocol and consent.

All subjects will undergo a verbal screen, and if they are eligible and sign a medical release form, their medical records will be obtained to confirm their medical history. After consenting, demographic data, gravidity, parity, and body mass index (BMI) will obtained. The patient's physician will be notified of participation in the study and have access to the laboratory results.

Eligibility:

Inclusion criteria:

-include diagnosis of gestational diabetes during recent pregnancy (4-16 weeks)
-age 18 or older.
-written informed consent

Exclusion criteria:

- pregestational diabetes (type 1 or type 2)
- include known known skin adhesive allergy which would prevent subject from wearing a CGM,
-history of bariatric surgery or other surgeries that induce malabsorption
-long-term use (>2 weeks) of systemic steroids during the testing interval
-inability or refusal to comply with protocol

For study participants, a Dexcom G7 CGM (Dexcom, Inc., San Diego, CA, United States) in blinded mode (participant unable to see the glucose values) will be worn for 10 days. Dexcom G7 CGM sensor measures interstitial glucose concentrations every 5 minutes. Insertion of the sensor will require an additional hospital visit for DEXCOM placement and women will be offered flexibility in scheduling to assist compliance. Trained research personnel will assist in implanting the sensors. Neither participants nor professionals will have access to the glucose measurements during sensor use. The Dexcom G7 sensors will be removed after 10 days and returned to study coordinator. All participants will receive a $100 incentive for participation in the trial

HbA1c, Fructosamine and OGTT data

We will use the glucose levels and HbA1c values as defined by the American Diabetes Association (ADA) guidelines(8) for the diagnosis of normal, prediabetes, and type 2 diabetes. Following the guidelines of ADA, a fasting blood glucose (FBG) below 126 or 2-h blood glucose (2hBG)< 140 mg/dl is considered normal glucose tolerance; FBG of 100-125 mg/dl or 2-h blood glucose (2hBG) ≥ 140- 199 mg/dl is classified as prediabetes, and FBG above or equal to 126 mg/dL or 2-h blood glucose (2hBG) ≥ 200 mg/dl in a standard oral glucose tolerance test (OGTT) as diabetic. The reference ranges for HbA1c results are:

- No diabetes: below 5.7%
- Borderline/prediabetes: 5.7% to 6.4%
- Diabetes: 6.5% or higher (8)

Fructosamine results may be considered alongside the HbA1c and other tests.

- In non-diabetics with normal albumin, fructosamine levels normally range between 175-265umol/L (micromoles per liter). For people with uncontrolled diabetes, the fructosamine range is 268-870 millimoles per liter (mmol/L). The concentrations of fructosamine corresponding prediabetes and diabetes clinical cut-points of 5.7% and 6.5% for HbA1c, based on percentiles, were 241.4 umol/L (the 77.1 percentile) and 270.2 umol/L (the 96.5 percentile), respectively (36).

Collection of glucose data The blinded glucose monitoring data on glycemia will be retrospectively assessed. The participant data collected from the CGM (Dexcom G7) will be downloaded with the Dexcom G7 reader and uploaded to Dexcom CLARITY

The percentage of time-in-target range, time hypoglycemia, and time hyperglycemia will be reported as either means with standard deviations (SD) or medians with interquartile ranges (IQR), depending on variable distribution. For analyses assessing overnight glycemia, daytime is defined as 5:00 AM to 11:59 PM and nighttime as 12:00 midnight to 4:59 AM

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Statistical analysis

Statistical analyses will be performed using SPSS version 15.1 for Windows (SPSS, Inc.; Chicago, IL). Continuous variables will be tested for normality of distribution using the Kolmogorov-Smirov test. When necessary, non-normally distributed data will be subjected to logarithmic or square-root transformation to obtain a normal distribution where necessary for subsequent analyses. Continuous parameters will be given as means ± standard deviations or medians with interquartile ranges (IQR). Results will be presented as mean ± standard deviation for normally distributed continuous variables and as medians, with the 25th and 75th IQR for non-normally distributed variables. Categorical data will be presented as percentage. Pearson correlation coefficient (r) and the significance for it (p) will be calculated between the variables. The chi square test will be used to compare categorical variables. Chi-square test will be used to test differences in percentage proportionality Student t tests will be used to compare normally distributed groups; otherwise, Mann-Whitney rank sum tests will be used. Multiple groups will be compared using Kruskal-Wallis one-way ANOVA with a Dunn's test for pairwise comparisons when appropriate. A two-sided P-value < 0.05 is considered statistically significant.

References

1. Metzger BE. Long-term outcomes in mothers diagnosed with gestational diabetes mellitus and their offspring. Clin Obstet Gynecol 2007; 50: 972-979
2. Kim C et al. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. Diabetes Care 2002; 25: 1862-1868 1
3. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet 2009; 373:1773–1779.
4. Vounzoulaki E, Khunti K, Abner SC, Tan BK, Davies MJ, Gillies CL. Progression to type 2 diabetes in women with a known history of gestational diabetes: systematic review and meta-analysis. BMJ 2020; 369: m1361 3.
5. Rayanagoudar G, Hashi AA, Zamora J, Khan KS, Hitman GA, Thangaratinam S. Quantification of the type 2 diabetes risk in women with gestational diabetes: a systematic review and meta-analysis of 95,750 women. Diabetologia 2016; 59: 1403–1411.
6. Ratner RE. Prevention of type 2 diabetes in women with previous gestational diabetes. Diabetes Care 2007; 30 (Suppl 2): S242-S245
7. Järvelä IY et al. Gestational diabetes identifies women at risk for permanent type 1 and type 2 diabetes in fertile age: predictive role of autoantibodies. Diabetes Care 2006; 29: 607-612.
8. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2022. Diabetes Care 2022; 45(Supplement_ 1): S17-S38.
9. Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin. Chem. 2002; 48(3):436–472.
10. Carson MP, Frank MI, Keely E. Original research: postpartum testing rates among women with a history of gestational diabetes – systematic review. Prim Care Diabetes 2013; 7: 177–186.

11. Bennett WL, Ennen CS, Carrese JA, et al. Barriers to and facilitators of postpartum follow-up care in women with recent gestational diabetes mellitus: a qualitative study. J Womens Health 2011; 20: 239–245
12. Werner EF, Has P, Kanno L, Sullivan A, Clark MA. Barriers to postpartum glucose testing in women with gestational diabetes mellitus. Am J Perinatol. 2019; ;36(2):212-218
13. Yahav L, Salem SY, Sandler-Rahat H, Baumfeld Y, Kaul K, Weintraub AY, Eshkoli T. Factors associated with compliance to the recommendations for postpartum diabetes mellitus screening among women with gestational diabetes mellitus. Arch Gynecol Obstet. 2023; 307(3):709-714
14. Nielsen JH, Olesen CR, Kristiansen TM, Bak CK, Overgaard C. Reasons for women's non-participation in follow-up screening after gestational diabetes. Women Birth 2015; 28(4):e157–63.
15. Paez KA, Eggleston EM, Griffey SJ, Farrar B, Smith J, Thompson J, et al. Understanding why some women with a history of gestational diabetes do not get tested for diabetes. Womens Health Issues 2014;24(4):e373–9.
16. McGovern A, Butler L, Jones S, van Vlymen J, Sadek K, Munro N, Carr H, de Lusignan S. Diabetes screening after gestational diabetes in England: a quantitative retrospective cohort study. Br J Gen Pract. 2014; 64(618):e17-23
17. Van Ryswyk EM, Middleton PF, Hague WM, Crowther CA. Women's views on postpartum testing for type 2 diabetes after gestational diabetes: Six-month followup to the DIAMIND randomised controlled trial. Prim Care Diabetes 2016;10(2): 91–102.
18. Russell MA et al. Rates of postpartum glucose testing after gestational diabetes mellitus. Obstet Gynecol 2006; 108: 1456-1462
19. Kim C et al. Risk perception for diabetes among women with histories of gestational diabetes mellitus. Diabetes Care 2007; 30: 2281-2286
20. Bunn HF, Haney DN, Kamin S, Gabbay KH, Gallop PM. The biosynthesis of human hemoglobin A1C: slow glycosylation of hemoglobin in vivo. J Clin Invest 1976; 57: 1652–1659.

21. International Expert Committee International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care. 2009; 32:1327–1334.
22. World Health Organization. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus Abbreviated Report of a WHO Consultation. WHO/NMH/CHP/CPM/; 2011: 11.1.
23. Kilpatrick ES. Problems in the assessment of glycaemic control in diabetes mellitus. Diabetes Med 1997; 14: 819–31.
24. Goldstein DE, Little RR, Lorenz RA, Malone JI, Nathan DM, Peterson CM. Tests of glycemia in diabetes. Diabetes Care. 2003; 26 (Suppl 1): S106–108.
25. Parrinello C.M., Selvin E. Beyond HbA1c and glucose: The role of nontraditional glycemic markers in diabetes diagnosis, prognosis, and management. Curr. Diab. Rep. 2014;14:548.
26. Rasche FM, Ebert T, Beckmann J, et al. Influence of erythropoiesis-stimulating agents on HbA1c and fructosamine in patients with haemodialysis. Exp Clin Endocrinol Diabetes 2017;125:384–39.
27. Danese E, Montagnana M, Nouvenne A, Lippi G. Advantages and pitfalls of fructosamine and glycated albumin in the diagnosis and treatment of diabetes. J Diabetes Sci Technol 2015 ;9:169–176.
28. Schleicher ED, Olgemöller B, Wiedenmann E, Gerbitz KD. Specific glycation of albumin depends on its half-life. Clin Chem. 1993 ;39:625-628.
29. Rodriguez-Segade S, Lojo S, Camiña MF, Paz JM, Del Río R. Effects of various serum proteins on quantification of fructosamine. Clin Chem. 1989;35:134-138.
30. Lee I, Probst D, Klonoff D, Sode K. Continuous glucose monitoring systems- Current status and future perspectives of the flagship technologies in biosensor research. Biosens Bioelectron 2021; 181:113054.
31. Wei W, Zhao S, Fu SL, Yi L, Mao H, Tan Q, et al. The association of hypoglycemia assessed by continuous glucose monitoring with cardiovascular outcomes and mortality in patients with type 2 diabetes. Front Endocrinol (Lausanne) 2019; 10: 536.

32. Gáborová M, Doničová V, Bačová I, Pallayová M, Bona M, Peregrim I, Grešová S, Štimmelová J, Dzugasová B, Šalamonová Blichová L, Donič V. Glycemic variability and risk factors of pregnant women with and without gestational diabetes mellitus measured by continuous glucose monitoring. Int J Environ Res Public Health. 2021; 18(7):3402.
33. Wei Q, Sun Z, Yang Y, Yu H, Ding H, Wang S. Effect of a CGMS and SMBG on maternal and neonatal outcomes in gestational diabetes mellitus: a randomized controlled trial. Sci Rep. 2016 27;6:19920.
34. Voormolen DN, DeVries JH, Sanson R, Heringa MP, de Valk H, Kok M, et al. Continuous glucose monitoring during diabetic pregnancy (GlucoMOMS): a multicentre randomized controlled trial. Diab Obes Metabol. 2018; 20:1894–902.
35. Yu F, Lv L, Liang Z, Wang Y, Wen J, Lin X, et al. Continuous glucose monitoring effects on maternal glycemic control and pregnancy outcomes in patients with gestational diabetes mellitus: a prospective cohort study. J Clin Endocrinol Metab. 2014; 99:4674–82.
36. Selvin E, Warren B, He X, Sacks DB, Saenger AK. Establishment of community-based reference intervals for fructosamine, glycated albumin, and 1,5-anhydroglucitol. Clin Chem 2018; ;64(5):843-850.