Real-time continuous glucose monitoring for the treatment of gestational diabetes: a randomized trial.

Principal Investigator: Malgorzata Mlynarczyk, MD, PhD
Andrew Lane, MD
Margarita de Veciana,MD
Alfred Abuhamad, MD

Specific Aims/Objectives of the study

- We seek to determine the effect of adding real-time continuous glucose monitoring (CGM) to standard treatment (dietary intervention, self blood glucose monitoring (SMBG), medications (oral anti-hyperglycemics, insulin) of gestational diabetes (GDM) on glycemic control in pregnancy.
- We hope to learn how the additional data and feedback provided by real-time CGM will affect a patient's glycemic control.
- We believe that this additional real-time data and constant feedback provided by CGM will improve the patient's glycemic control.

Abstract

Gestational diabetes (GDM) is a condition of carbohydrate intolerance with onset or first recognition in pregnancy. The prevalence of GDM is as high as 25% in some populations and continues to rise with the increase in obesity and type-2 diabetes. GDM places the pregnancy at great risk to both the mother and the neonate. Recent studies have proven that interventions including dietary and medications lower the risk to the pregnancy. Both the American College of Obstetrics and Gynecology (ACOG) and the American Diabetes Association (ADA) recommend dietary interventions with daily glucose monitoring as the initial treatment of choice. Meanwhile, outside of pregnancy, promising new technologies such as continuous glucose monitors (CGM) are revolutionizing diabetic care. We seek to determine if the constant feedback of a real-time CGM system would improve glycemic control compared to traditional management in GDM.

Background and rationale

Gestational diabetes mellitus (GDM) is a condition of carbohydrate intolerance with onset or first recognition in pregnancy and represents 90% of cases of diabetes in pregnancy.[1] The prevalence of GDM has increased to 5.6 % of pregnancies in 2009 and can be as high as 25% in some minority populations.[2,3] The prevalence is expected to continue to rise in step with increasing obesity and type-2 diabetes mellitus (DM) rates in reproductive aged women.[4]

GDM places both the mother and her fetus at risk. Known obstetric complications include: gestational hypertension, preeclampsia, and cesarean delivery. While known fetal and neonatal complications include, but are not limited to: macrosomia, operative delivery, shoulder dystocia, birth trauma, neonatal hypoglycemia, and hyperbilirubinemia.[1] Up to 50% of women with GDM will go on to develop type-2 diabetes mellitus in the next 25 years.[5] GDM increases the offspring's risk of developing obesity, impaired glucose tolerance, and metabolic syndrome later in life.[6-8]

There is graded linear association between hyperglycemia and adverse outcomes[9]. Large trials have confirmed that treatment of GDM to optimize glycemic control can decrease the incidence of many of these associated adverse outcomes.[10-12] An estimated 15-30% of women will not be able to maintain "adequate" glycemic control with these interventions alone, necessitating pharmacologic therapy with either insulin or oral agents.[13]

Hyperglycemia leads to adverse pregnancy outcomes. Recent studies have reported a graded linear association between maternal hyperglycemia and adverse perinatal outcomes across the glucose spectrum. The Hyperglycemia and Adverse Pregnancy Outcome study was a large international multicenter study, which demonstrated a continuous relationship between maternal

hyperglycemia and cesarean delivery, birth weight > 90%, neonatal hypoglycemia, and fetal hyperinsulinemia.[9]

It is now conclusive that treatment of GDM improves outcomes. The 2005 Australian Carbohydrate Intolerance in Pregnant Women study was the first large trial to show this relationship. The investigators randomized 1,000 women to either a treatment group (dietary counseling, blood glucose monitoring, and insulin therapy as needed) or to routine care (no interventions). Treatment led to a significant reduction in the primary composite outcome of perinatal death, shoulder dystocia, and birth trauma (fracture, nerve palsy). Treatment also reduced the frequency of large for gestational age (LGA) infants, birth weight > 4,000g, and preeclampsia. 20% of patients in the treatment group required insulin. Oral medications were not used.[10]

This was followed by a 2009 randomized trial by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network in the United States. This trial randomized 958 women with mild GDM (fasting glucose level < 95 mg/dL and 50-g glucose screen values of 135 – 200 mg/dL) to either treatment (dietary interventions, glucose monitoring, and insulin therapy if needed) or routine care (no interventions). They did not see a significant difference between the groups in the primary composite outcome of perinatal death, neonatal hypoglycemia, elevated umbilical cord C-peptide level, or birth trauma. They did see a reduction in the secondary outcomes of birth weight, LGA infants, neonatal fat mass, cesarean delivery, shoulder dystocia, and hypertensive disorders of pregnancy. Only 7.7% required insulin therapy.[11]

A 2013 systematic review and meta-analysis for the US Preventative Services Task Force, which included both of these studies, assessed the effects of treatment with nutritional therapy, glucose monitoring, and insulin as needed. Five randomized control trials and six cohort studies with a total of 2,272 patients were included. The authors concluded that treatment reduced the incidence of birth weight > 4,000 g, shoulder dystocia, and preeclampsia.[12]

The optimal frequency of blood glucose monitoring for GDM has not been determined. Most advocate for several measurements a day, usually fasting, and 1-2 hour post prandial values after each meal. Modern home glucose meters used for SMBG use test strips containing the enzyme glucose oxidase. The capillary blood glucose interacts with glucose oxidase and an electrode inside the meter measures the electrical signal generated by the reaction. Most commercial meters are reasonably accurate to within +/- 10% of plasma values.[14]

CGM systems involve the subcutaneous insertion of an electrode impregnated with glucose oxidase. Much like the SMBG the CGM measures the electrical activity of glucose with glucose oxidase. However, CGM systems measure the glucose of interstitial fluid instead of capillaries as they do to pierce blood vessels.[15] The accuracy of CGM continues to improve. An evaluation of over 60,000 paired CGM and meter values type-1 DM showed 75% of readings were within 20% of the reference meter.[16]

Continuous glucose monitoring systems (CGM) measure interstitial glucose levels 288 times a day. CGM is well tolerated in pregnancy and better able to detect GDM patients needing pharmacologic intervention than SMBG.[17] CGM leads to better glycemic control in the third trimester, lower birth weight, reduced risk of macrosomia in pregestational diabetics.[18] It also provides a more objective method of glycemic control than self-monitoring, where pregnant women falsify 8 – 36% of values.[18]

Newer CGM systems are able to transmit real time glucose values to a paired electronic display as either a stand-alone system or as part of a insulin pump. We have been unable to find any published studies using real-time CGM systems for the management of GDM. We sought to determine if the constant feedback of a real-time CGM system would improve glycemic control compared to traditional management in GDM.

A Cochrane review has determined that at this time there is not enough evidence to determine the best method of measuring glucose values for pregnant patients with DM.[19] Hemoglobin A1C values are not as useful in the pregnant population. Due to increased red blood cell turnover and dilutional anemia, the value will be falsely lowered.[13] Additionally, it is unable to identify postprandial hyperglycemia, which is linked to macrosomia, neonatal hypoglycemia, and cesarean delivery.[20]

Yogev was the first to evaluate CGM in pregnancy in 2003.[21] The study used CGM for 72 hours on 8 patients with GDM or pregestational diabetes on insulin to make dosage adjustments. In 2004 Porter used CGM in 20 patients without GDM and compared them 20 diabetic pregnant patients.[22] Mclachlan offered patients with GDM or pregestational diabetes the option of adding CGM to their standard care.[23] Fifty women requested CGM for a 72 hour tracing of CGM. Clinicians in the study found that 62% of the CGM tracing provided additional clinical information that altered clinical management and 77% of the women believed that the benefits of CGM outweighed the inconvenience of wearing the device. Kestiela compared CGM to SMBG for 48 hours in 73 Finish GDM patients.[17] They believed that CGM may be better at identifying patients who require medication than SMBG. In 2008 Muphy completed a randomized trial in 71 pregestational diabetic patients comparing SMBG and interval CGM to SMBG in pregnancy and showed that the addition of interval CGM improved glycemic control, reduced the risk of macrosomia, lowered the birth weight, and lowered the A1C values after 32 weeks gestation.[18] In 2014, Yu compared SMBG to SMBG with interval CGM in 340 women with GDM in China.[24] They did not show a significant difference in mean blood glucose. However they did show significantly lower standard deviations of blood glucose, mean amplitude of glycemic excursions, as well as lower rates of preeclampsia, primary cesarean delivery, and birth weight. Finally, in 2016 Alfadhli compared 130 women with GDM and either SMBG or SMBG with CGM.[25] Using SMBG data only, they did not see a difference in glycemic control or perinatal outcomes.

Our proposed study will add new information to the emerging use of CGM in pregnant women with GDM. First, most studies only use CGM for 48 – 72hours at a time, while we will be using CGM for 7 day intervals. Both groups will use the same Enlite sensor (Medtronic). The blinded CGM group we will be using the Medtronic iPro2 system (Enlite sensor + transmitter). The real-time CGM group we will be using the 530g system (iPro2 (Enlite sensor + transmitter) + inactivated 530g pump set only to display glucose values, no insulin will be administered). This CGM system has been FDA approved to for up to 7 days between sensor changes.[26,27] Second, no previous study has used real time CGM in pregnant patients with GDM in the US. We will be the first to describe the use of this technology in this patient population. Third, most of these trials have been performed on populations that are not representative of our patient population at EVMS. This will be the largest US study of CGM in GDM. Fourth wearable medical and fitness technology is already popular, but as both the technology and the demand continues to grow, it will become the future of diabetes management. Studies have already shown that real time CGM is an effective educational and motivational tool in type-1 and type-2 DM.[28,29]

Research Design and Methods

Subject population

- Subject will be recruited from the EVMS MFM clinics at the main campus (Hofheimer Hall) and Sentara Princess Anne campus. No international sites will be covered by EVMS IRB approval.
- This protocol has been solely developed by EVMS researchers

Inclusion criteria:

- Maternal age 18-45
- Singleton gestation
- Gestational age < 32 weeks gestation at study inclusion
- BMI $\leq$ 45

- 50g glucose challenge: ≥ 135 mg/dL
- 100 g 3 hr OGTT: ≥ 2 abnormal values using the Carpenter Coustan cut offs (fasting ≥ 95 mg/dL, 1 hr ≥ 180 mg/dL, 2 hr ≥ 155 mg/dL, 3 hr ≥ 140 mg/dL)
- Attended the MFM diabetes education class

Exclusion criteria:

- Maternal age <18, >45
- Multi-fetal gestation
- Gestational age ≥ 32 weeks study inclusion
- BMI > 45
- Pregestational diabetes
- Gestational diabetes diagnosed before 24 weeks
- Did not Attend the diabetes education class
- Known fetal anomaly
- Known fetal aneuploidy
- Required ongoing treatment with medications that can exacerbate hyperglycemia: steroids, hydroxyprogesterone caproate injections (Makena), HARRT HIV medications
- Learning disability
- Concern for non compliance with medical care
- Imminent preterm delivery due to maternal disease or fetal conditions
- Is not willing to wear CGM

Demographic information collected:

- Maternal age at enrollment (years)
- Gestational age at diagnosis of GDM (weeks)
- Gestational age at study inclusion (weeks)
- Gravidty and parity (G_P_ _ _ _)
- Race or ethnic group (self reported, Black, White, Asian, Hispanic, Other)
- Smoking status (current use in pregnancy at time of enrollment, yes/no)
- Alcohol use (current use in pregnancy at time of enrollment, yes/no)
- BMI at study entry (weight in kg / height in m^2)
- History of GDM in a prior pregnancy (yes/no)
- Result of 50g OGTT (mg/dL)
- Results of 3hr 100 g OGTT (mg/dL)
- A1C at time of enrollment
- Other comorbidities including but not limited to: hypertension, autoimmune disease, thyroid dysfunction, polycystic ovarian syndrome, cardiac disease, pulmonary disorders, thromboembolic disorders

Vulnerable populations:

- We will not involve vulnerable populations such as those < 18 years old, prisoners, or mentally impaired in this study.

Study design

- Hypothesis:
  - The increased data and feedback provided by real-time CGM will improve glycemic control in gestational diabetic patients over routine SMBG.
- Primary Outcome:
  - Mean blood glucose (mg/dL) in the real-time CGM group compared to SMBG group during the 4^{th} week of study from data collected on the 6 day of CGM use during that week.
- Covariates
- Glycemic outcomes:
  - Between Groups -Failed dietary therapy (started on medication), time spent in normoglycemia week 1 vs. week 4 (min/day), time spent in hyperglycemia week 1 vs. week 4 (min/day), time spent in hypoglycemia week 1 vs. week 4 (min/day)
  - Within Groups - Time spent in normoglycemia week 1 vs. week 4 (min/day), time time spent in hyperglycemia week 1 vs. week 4 (min/day) , time spent in hypoglycemia week 1 vs. week 4 (min/day)
- Maternal outcomes :

- BMI at time of delivery (kg/m^2)
- Gestational hypertension (defined as SBP $\geq$ 140 mm Hg or DBP $\geq$ 90 mmg Hg, on 2 occasions at least 4 hrs apart)
- Preeclampsia (defined as gestational hypertension plus either new-onset proteinuria ($\geq$ 300 mg/24 2hrs, protein:creatinine $\geq$ 0.3 mg/dL), thrombocytopenia (platelet count < 100,000/uL), elevated AST or ALT (> 2x upper limit of normal), renal insufficiency (serum creatinine > 1.1 mg/dL or an unexplained doubling of creatinine), pulmonary edema, or cerebral or visual symptoms
- HbA1C values week 1 compared to week 4 (%)
- Polyhydramnios (MVP $\geq$ 8 cm at any point in the pregnancy)
- Cesarean delivery (w/ indication: macrosomia, malpresentation, failed induction, fetal distress, failed TOLAC, scheduled repeat, other)
- IOL (w/ indication)
- Operative vaginal delivery (yes/no) an type (forceps/vacuum)
- Shoulder dystocia (diagnosed clinically)
- Fetal macrosomia ($\geq$ 4,000g at 38 wk u/s)
- 3rd or 4th degree perineal laceration at time of delivery

- Neonatal outcomes:
  - Gestational age at delivery (weeks, days)
  - Preterm delivery (< 37 weeks gestational age at birth)
  - Birth weight (grams)
  - Perinatal morbidity composite outcome:
    - Hypoglycemia (yes/no): < 2 hrs after birth and before feeding, defined as < 35mg/dL
    - Hyperbilirubinemia (yes/no): collected 16-36 hrs after birth, defined as > 95% for any given point after birth requiring phototherapy according to AAP guidelines
    - Birth trauma (yes/no): brachial plexus injury or clavicular, humeral, or skull fracture
    - Intrauterine fetal demise or neonatal death (yes/no): prior to hospital discharge
  - Large for gestational age (yes/no): defined as birth weight > 90%
    - Term infants ($\geq$ 37'0) WHO 0-24 months growth charts
      - Boys = > 4,011 g
      - Girls = > 3,852 g
    - Preterm infants (< 37'0) Fenton preterm growth charts
      - Use online calculator with actual gestational age
  - Small for gestational age (yes/no): defined as birth weight < 10%
    - Term infants ($\geq$ 37'0) WHO 0-24 months growth chart
      - Boys = < 2,758 g
      - Girls = > <2,678 g
    - Preterm infants (< 37'0) Fenton preterm growth charts
      - Use online calculator with actual gestational age
  - Admission to NICU (yes/no) and length of NICU stay (days)
  - Respiratory distress syndrome (defined as need to supplemental oxygen > 4 hrs after birth)
- Randomization scheme:
  - 40 index cards will be labeled. 20 will have an allocation to one group written on them and the other 20 will have an allocation for the other group written on them for an even number in each group. Each index card will be placed into its own opaque ("security") envelope and sealed. Then the research coordinator will shuffle all envelopes. The research coordinator will label each envelope sequentially from 1 to 40. This number will ensure the generated randomization scheme is maintained and the number will also serve as the participant's study ID. The envelopes will be secured in a locked cabinet in the research office when

not needed. Only after a participant has been enrolled into the study will an envelope be opened and the patient allocated to a group.

Procedures

- Procedures
- Dr. Lane will review charts of new Gestational Diabetes patients whom are scheduled to attend the gestational diabetes classes at Eastern Virginia Medical School (Mondays) and EVMS Sentara Princess Anne MFM Clinic (Fridays). He will select those patients who meet the study criteria based on the inclusion/exclusion of the study. He will then give that information to Research Coordinator, Joanne Audouin. Joanne will call patients a day before their scheduled Diabetes class to discuss this study. If patient agrees to participate, Joanne will meet them right before class to enroll (review and sign consent forms). Dr. Lane will do the same for Sentara Princess Anne patients.
- Patients will be randomized to two arms: Traditional Management (20 patients); using the Ipro2 CGM and CGM management (20 patients); using the "real time" CGM. Joanne will randomize patients in arms according to names drawn from an envelope during the time of consent. Research activities will occur at standard of care clinical visits. Patients are required to attend research study visits every 7 days for 4 weeks.
- During each visit data such as demographic data, glycemic levels, primary and secondary maternal and neonatal outcomes will be collected. At each visit CGM will be downloaded, a new sensor will be placed for the next 7 days, clinicians will manage GDM per EVMS GDM protocols, and DM will provide dietary reviews/education. Joanne will download CGM, add interval data points to database and replace CGM for EVMS patients. Dr. Lane will do the same for EVMS Sentara (Princess Anne) patients. Data will be printed and transferred to data collection sheets. All data from the forms will be uploaded into a de-identified electronic database (Redcap, EVMS, set up by EVMS CHAD). All forms will be placed in the patient's research folder.
- Patients charts will be kept locked in a file cabinet in the research coordinator's office. Only members of the study will have access to this file cabinet.
- Outcome data will be collected at the completion of study. The data from the CGM reports will not be shared with the clinical provider during the clinic visits.
- Both Dr. Lane and Joanne will receive training on both devices from a local Medtronic representative. They will then educate the patients on the proper use and function of these devices at the time of enrollment.
- Both CGM devices are FDA approved and produced by Medtronic. Each measures 288 glycemic values/day. The ipro2 blindly collects values w/o a screen so the patient is not aware of the data. The 530g CGM has a screen that displays the values that the patient can see. Both groups will also perform SMBG. SMBG is used to calibrate the CGM and for the clinician's review to make clinical decisions.
- Joanne and Dr. Lane will be each other's backups.
- Group 1: real-time CGM for 4 weeks with weekly clinic visits
- Group 2: blinded CGM for 4 weeks with weekly clinic visits
- If possible, provide a step-by-step account of each stage of your study. See attached PDF flow sheet
- Demographic data will be collected on forms at study inclusion. Outcome data will be collected on forms at study completion. Weekly CGM data will be downloaded by a study investigator and the data will be printed and transferred to forms. All forms will be placed in the patient's research folder. All data from the forms will be uploaded into a de-identified electronic database (Redcap, EVMS, set up by EVMS CHAD).
- We will be collecting the demographic, primary outcome, maternal/neonatal/glycemic secondary outcome data as outlined above
- All study investigators and the research coordinators will have access to the research folders that include identifying information on study subjects. These folders will be kept in

a locked file cabinet in the locked office of the research coordinator. No one else will have access to this data.

Risk

- There are very few known risk to patients involved in this study, beyond what we would normally expect from any pregnancy with gestational diabetes. Risks and side effects related to continuous glucose monitors (CGM) include skin irritation at the sensor site, infection at the sensor site and pain at the sensor site.
- Study team will inform each patient enrolled on this study of these risks during the review of the informed consent. Research team will ensure patient has access to the investigator and research coordinator's telephone number in the case of a side effect.
- If the patient experiences any issues with wearing the CGM device, it will be removed and she will not be required to wear another device (page 9 of application).
- There is a risk associated with allowing your data to be saved is the release of personal information from your study record. Research team members will strive to protect patient records such as name, address, social security number, phone number and will notify patient if information is breeched.

Statistical Analysis Plan

- Sample Size Calculations:
  - Estimated mean blood glucose of a pregnant women with GDM using CGM: 102.6 mg/dL +/- SD 9 mg/dL[24]
  - Randomized trial, 1:1 allocation, continuous variable outcome
  - Alpha = 0.05
  - Beta = 0.80
  - 10 patients/arm to detect a 20% decrease in mean blood glucose
  - Goal: 20 patients/arm with interim analysis after 10 patients/arm have completed the trial
- Other analysis will be with the guidance and aide of EVMS CHAD:
  - All data will be analyzed with intention to treat. Normality of data will be tested for all continuous variables using the Kolmogorov–Smirnov test. Normally distributed parameters will be presented as mean±SD, and non-normally distributed values are presented as median (range). Categorical data will be reported as frequency and percentage. Parametric (the Student's t-test) or nonparametric (the Mann–Whitney U-test) comparisons will be used based on the distribution of variables. The pre/post change in blood glucose between the two arms will be compared using regression models, when treatment group will be treated as a qualitative independent variable. To assess the significant difference between the two arms adjusting for covariates, ANCOVA model will be used.. A $p < 0.05$ will be accepted as statistically significant. SAS 9.4 (SAS Institute Inc, Cary, NC) will be used for statistical analysis.

REFERENCES:

1. Bulletins--Obstetrics CoP. Practice Bulletin No. 137: Gestational diabetes mellitus. *Obstet Gynecol.* 2013;122(2 Pt 1):406-416.
2. Moyer VA, Force USPST. Screening for gestational diabetes mellitus: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2014;160(6):414-420.
3. Correa A, Bardenheier B, Elixhauser A, Geiss LS, Gregg E. Trends in prevalence of diabetes among delivery hospitalizations, United States, 1993-2009. *Matern Child Health J.* 2015;19(3):635-642.
4. Wier LM WE, Burgess J, Elixhauser A. Hospitalizations related to diabetes in pregnancy. In.
5. England LJ, Dietz PM, Njoroge T, et al. Preventing type 2 diabetes: public health implications for women with a history of gestational diabetes mellitus. *Am J Obstet Gynecol.* 2009;200(4):365.e361-368.
6. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. *Pediatrics.* 2005;115(3):e290-296.
7. Malcolm JC, Lawson ML, Gaboury I, Lough G, Keely E. Glucose tolerance of offspring of mother with gestational diabetes mellitus in a low-risk population. *Diabet Med.* 2006;23(5):565-570.
8. Gillman MW, Rifas-Shiman S, Berkey CS, Field AE, Colditz GA. Maternal gestational diabetes, birth weight, and adolescent obesity. *Pediatrics.* 2003;111(3):e221-226.
9. Metzger BE, Lowe LP, Dyer AR, et al. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med.* 2008;358(19):1991-2002.
10. Crowther CA, Hiller JE, Moss JR, et al. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med.* 2005;352(24):2477-2486.
11. Landon MB, Spong CY, Thom E, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med.* 2009;361(14):1339-1348.
12. Hartling L, Dryden DM, Guthrie A, Muise M, Vandermeer B, Donovan L. Benefits and harms of treating gestational diabetes mellitus: a systematic review and meta-analysis for the U.S. Preventive Services Task Force and the National Institutes of Health Office of Medical Applications of Research. *Ann Intern Med.* 2013;159(2):123-129.
13. Association AD. 13. Management of Diabetes in Pregnancy. *Diabetes Care.* 2017;40(Suppl 1):S114-S119.
14. Freckmann G, Baumstark A, Jendrike N, et al. System accuracy evaluation of 27 blood glucose monitoring systems according to DIN EN ISO 15197. *Diabetes Technol Ther.* 2010;12(3):221-231.
15. Klonoff DC. Continuous glucose monitoring: roadmap for 21st century diabetes therapy. *Diabetes Care.* 2005;28(5):1231-1239.

16. Mastrototaro J, Shin J, Marcus A, Sulur G, Investigators SCT. The accuracy and efficacy of real-time continuous glucose monitoring sensor in patients with type 1 diabetes. *Diabetes Technol Ther.* 2008;10(5):385-390.
17. Kestilä KK, Ekblad UU, Rönnemaa T. Continuous glucose monitoring versus self-monitoring of blood glucose in the treatment of gestational diabetes mellitus. *Diabetes Res Clin Pract.* 2007;77(2):174-179.
18. Murphy HR, Rayman G, Lewis K, et al. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial. *BMJ.* 2008;337:a1680.
19. Moy FM, Ray A, Buckley BS. Techniques of monitoring blood glucose during pregnancy for women with pre-existing diabetes. *Cochrane Database Syst Rev.* 2014(4):CD009613.
20. de Veciana M, Major CA, Morgan MA, et al. Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. *N Engl J Med.* 1995;333(19):1237-1241.
21. Yogev Y, Ben-Haroush A, Chen R, Kaplan B, Phillip M, Hod M. Continuous glucose monitoring for treatment adjustment in diabetic pregnancies--a pilot study. *Diabet Med.* 2003;20(7):558-562.
22. Porter H, Lookinland S, Belfort MA. Evaluation of a new real-time blood continuous glucose monitoring system in pregnant women without gestational diabetes. A pilot study. *J Perinat Neonatal Nurs.* 2004;18(2):93-102.
23. McLachlan K, Jenkins A, O'Neal D. The role of continuous glucose monitoring in clinical decision-making in diabetes in pregnancy. *Aust N Z J Obstet Gynaecol.* 2007;47(3):186-190.
24. Yu F, Lv L, Liang Z, 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(12):4674-4682.
25. Alfadhli E, Osman E, Basri T. Use of a real time continuous glucose monitoring system as an educational tool for patients with gestational diabetes. *Diabetol Metab Syndr.* 2016;8:48.
26. FDA. iPro2 Continuous Glucose Monitoring System - P150029. 2016; https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm517304.htm. Accessed 8/8/17.
27. Sotelo J. In. Email ed.
28. Głowińska-Olszewska B, Tobiaszewska M, Łuczyński W, Bossowski A. Monthly use of a real-time continuous glucose monitoring system as an educational and motivational tool for poorly controlled type 1 diabetes adolescents. *Adv Med Sci.* 2013;58(2):344-352.
29. Yoo HJ, An HG, Park SY, et al. Use of a real time continuous glucose monitoring system as a motivational device for poorly controlled type 2 diabetes. *Diabetes Res Clin Pract.* 2008;82(1):73-79.