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Title

Assessment of Glucose Kinetics with Real-Time Continuous Glucose Monitoring during Labor

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Running head: Glucose kinetics using CGM during labor

Abstract

Title

Assessment of Glucose Kinetics with Real-Time Continuous Glucose Monitoring during Labor

Aim: Changes in glucose levels during labor have not been sufficiently investigated in pregnant women. Using real-time continuous glucose monitoring, we aimed to assess glucose kinetics during labor among pregnant women with gestational diabetes mellitus (PwGDM), and those with normal glucose tolerance (PwNGT).

Methods: Japanese PwGDM and PwNGT who had planned a transvaginal delivery at Okayama University Hospital were enrolled. The correlation between changes in glucose levels during labor among the PwGDM and PwNGT groups at four time periods was assessed: (i) active phase of 1st stage of labor; (ii) 2nd stage of labor; (iii) postpartum 0–12h; and (iv) postpartum 12-48h.

Results: In total, 18 and 22 PwGDM and PwNGT, respectively, were enrolled. During labor, both groups had similar changes in glucose levels over time, which peaked during period 3. The main effect of glucose level changes was the labor period ($P<0.001$), not the presence of gestational diabetes mellitus. Furthermore, differences in glucose levels in the PwGDM group were observed between periods 1 and 2 ($P=0.037$), 1 and 3

(P=0.024), 3 and 4 (P=0.005); differences in glucose levels in the PwNGT group were observed between periods 3 and 4 (P=0.024).

Conclusions: During labor, both PwGDM and PwNGT groups showed similar changes in glucose levels over time. During delivery, the PwGDM who regularly measured their own glucose levels could be managed using the same nutritional management methods as those for PwNGT.

Keywords: continuous glucose monitoring; during labor; gestational diabetes mellitus; glucose level; pregnancy

Introduction

According to the International Association of Diabetes and Pregnancy Study Groups (IADPSG), the frequency of gestational diabetes mellitus (GDM) has increased by fourfold in Japan since 2011 and has increased by 19.4% in the United States.[1, 2] As such, the management of patients with GDM during pregnancy and labor has become an imperative issue in healthcare. Both the Japanese and American guidelines recommend that the blood glucose (BG) levels of pregnant women with GDM (PwGDM) be maintained at 70–110mg/dL during pregnancy or at 120mg/dL during labor. [3, 4]

As continuous glucose monitoring (CGM) levels can be recorded on a device every 5min, changes in glycemic trends, such as hyperglycemia and hypoglycemia, which may have been previously overlooked during self-monitoring of blood glucose (SMBG), can now be assessed. Furthermore, changes in the mother's glucose levels (GL) can be improved during pregnancy using CGM; such improvements can reduce the risk of maternal-fetal complications.[5–7] Sensor glucose (SG) measures GL from the interstitial fluid surrounding the subcutaneous tissue cells so that it is possible to detect differences in the accuracy between the SG and the SMBG levels.[8] However, changes in GL during labor have not been sufficiently investigated in PwGDM or

pregnant women with normal glucose tolerance (PwNGT). Therefore, this study aimed to clarify the changes in GL during labor in PwGDM and PwNGT.

Methods

Ethical Statements

This study was approved by the ethics committee of Okayama University (April 2016, approval number 1604-035) and conforms to the provisions of the Declaration of Helsinki, as revised in Fortaleza, Brazil on October 2013. Informed consent was obtained from all patients.

Study Design, Patients, and Data

In this case–control study, Japanese PwGDM (all cases) and PwNGT (random cases) who had planned a transvaginal delivery from May 2016 to March 2018 at Okayama University Hospital were enrolled. Pregnant women whose babies were delivered before data collection began, whose delivery method was changed to cesarean section during measurement, or who were not attached to any measurement device because of in sufficient measuring devices during over lapping deliveries were excluded. Pregnant women who were taking any psychotic medication or steroids up

until delivery, had labor complications, or for whom there were other reasons they were unable to undergo examinations, and who were already on continuous insulin treatment during pregnancy, were also excluded. Patient characteristics, such as age, height, pre-pregnancy weight, body mass index (BMI), pre-delivery weight, total weight gain during pregnancy, body temperature on admission, time of first or second labor stages, age of gestation at delivery, and effacement, station, and Bishop score at device installation were collected. Additionally, data were collected on primiparity, family history of diabetes, vacuum extraction, the use of epidural anesthesia for delivery, and the induction of labor. The patient selection flowchart is shown in Figure1. BG dynamics during parturition were extrapolated on the assumption that it continued until after parturition. Based on previously published studies, [9–11] the estimated mean BG levels during parturition in the PwGDM and PwNGT groups were 90 and 110mg/dL, respectively. Based on published data, [10,11] we used α of 0.05 and β of 0.20. Additionally, we used 20mg/dL as the standard deviation for each group. Thus, 17 cases, in each group, were required for the statistical test. Integrated statistics software STATA (Stata Corp LLC) was used for the analysis.

Diagnosis and Management of GDM

Patients underwent a 2-h 75-g oral glucose tolerance test (OGTT) as recommended by the Japan Society of Obstetrics and Gynecology.[12] GDM was defined according to the criteria outlined by the IADPSG, and the OGTT results were used to identify women with GDM as recommended by the Japanese Society of Diabetes and Pregnancy (JSDP). [13] All pregnant women in the study were followed up according to a routine pregnancy care program: hospital visits every 4weeks until 26 weeks, every 2 weeks until 36 weeks and weekly after 36weeks of pregnancy. During the first week after diagnosis of GDM, self-monitored plasma glucose measurements were recommended 4–7 times daily according to the risk of GDM (e.g., four times daily meant before breakfast and 2 h after each main meal, whiles even times daily included additional checks before lunch and dinner, and at bedtime). Additionally, nutritional guidance was provided every 4weeks, while insulin doses were adjusted with the assistance of an experienced diabetologist every 2 or 4weeks.

Real-Time CGM and SMBG

Medtronic Minimed 620G (CGM transmitter, Enlite Glucose Sensor; Care-link Pro) was used for real-time CGM measurements, while the Glutest Neo Super (Sanwa Kagaku Kenkyusho) was used for SMBG.[9, 14, 15] These devices are ISO certified, and thus,

the measurements were presumed to be highly accurate. Moreover, SG levels comparable to BG levels can be obtained using these devices.[16] CGM levels were measured via SG. The SG monitor was fitted on the upper, outer arm where, with greater amounts of subcutaneous fat, interference with the delivery would be unlikely. SMBG was performed using the arm on which the device was fixed. For all cases, the device was fitted on the patient during hospitalization, after contractions began, and once the rupture of membranes had been confirmed, or if labor was induced. SG was calibrated using BG levels obtained from SMBG as follows. In all cases, the first calibration was performed when the alarm rang, approximately 2 h after the CGM device was fitted. Thereafter, from the beginning of labor until the delivery of the baby, BG levels were measure data fixed time, at least 4 times daily, using SMBG. Once the baby was born and the postpartum procedures were completed, BG calibrations were taken at least two times daily. Changes in GL for the PwGDM and PwNGT groups were measured from the commencement of contractions until 48h after parturition. A sample of the CGM levels for one patient is shown in Figure2. Changes in GL from the activelaborphaseto48hafterparturitionforthePwGDMandPwNGTgroupsarerepresentedby theaverage GL for each period.

SG Measurements and Factors for Analysis

The 48-h period following parturition was divided into four time periods as follows: (i) active phase of 1st stage of labor (i.e., the active phase); (ii) 2nd stage of labor; (iii) postpartum 0–12h; and (iv) postpartum 12–48h. The active labor phase was defined as the time when the cervix was dilated by more than 4cm,100% effaced, and at −2 stations or more.[17]

GL dynamics were compared between the two groups by determining the mean GL for each group in each time window.

Delivery of PwGDM

This study adhered to the American College of Obstetricians and Gynecologists (ACOG) and JSDP management methods for deliveries among pregnant women with abnormal glucose metabolism.[16] Therefore, regarding the timing or amount of food eaten, PwGDM were allowed to eat or drink during labor within the limits of caloric management provided by the hospital. Subcutaneous in jection of fast-acting insulin was administered directly before food consumption (as directed by the doctor in charge) during the latent phase of labor or after the commencement of labor. Pre-meal insulin was discontinued following the active phase.

GL control was achieved before eating and drinking, using an insulin sliding scale, in line with hospital regulations. Hypoglycemia was defined as a GL <60mg/dL. In such

cases, the patient was either given food containing 5–10g of glucose or 150–200mL of soda. GL ≥70mg/dL but ≤150mg/dL required no treatment, while 1 unit of fast-acting insulin was administered subcutaneously for GL >150mg/dL. Thereafter, for each GL increase of 50mg/dL, 1 unit of fast-acting insulin was administered subcutaneously. The intravenous drips used for inducing labor and for newborn resuscitation at this hospital contained extracellular fluid (glucose content: 0%); thus, glucose was not loaded. For the PwGDM group, SMBG was continued during the postpartum period before and 2h after meals, and all insulin doses were then discontinued after 48h.

Statistical Analysis

The patient characteristics were compared using Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables, when appropriate. Continuous variables were reported as medians (ranges). Missing values in CGM data were replaced with the peripheral average values based on the levels at 5, 10 and 15min (30min in total) before and after the missing value. The GL differences during the progression of labor were examined using split-plot analysis of variance and post hoc tests (tests of within-subject effects) in the PwGDM and PwNGT groups. For the post hoc tests, unpaired and paired ttests were corrected using Bonferroni's method. The level of significance was set at 5%. All statistical analyses were performed using

IBM spss statistics version 23.0 (IBM Corp.), and a two-sided P-value <0.05 was considered statistically significant. A third-party organization, Suzuki Iryō Tōkei Services (Suzuki medical statistics services, https://medicalslide.jimdo.com/) used the data from this study for the above statistical analysis. The analysis was certified by Editage × Stagen (Supporting Information S1).

Results

Among the 93 pregnant women initially enrolled, 42 (45.1%) were excluded. Of the 51 women who had transvaginal deliveries, 25 (26.9%) and 26 (28.0%) were included in the PwGDM and PwNGT groups, respectively. In total, 8 of 93 (8.6%) women were further excluded due to missing data as well as two cases of overt diabetes during pregnancy and a case of diagnosis of type 1 diabetes after delivery. Finally, 40 patients (18 [19.4%] and 22 [23.6%] in the PwGDM and PwNGT groups, respectively) were included in the analysis (Figure.1). The patient characteristics as well as the newborn characteristics, including birth weight, height, chest measurement, umbilical cord blood gas, and the first blood sugar level, are shown in Table1. The prepregnancy body weight and BMI of women in the PwGDM were higher than those in the PwNGT group (P=0.047, 0.066). Total weight gain during pregnancy of women in the PwNGT were higher than those in the PwGDM group (P=0.0075). Among infants, the average first

BG measurement was significantly lower among infants whose mothers were in the PwGDM group, although it was above the cut-off for hypoglycemic GL (<50mg/dL). No significant difference was observed between the PwGDM and PwNGT groups in any of the other characteristics investigated.

In total, two (11.1%) patients required insulin during the latent phase of labor (before period 1); this decreased to zero patients after the active labor phase (period 1). No patient received insulin after period 2. Hence, the total amount of insulin used among all patients decreased from 14 units to 0 between the latent and the active phase. The details of the two cases that required insulin treatment after the initiation of labor pains are shown in Table 2.

Changes in GL from the active labor phase to 48h after parturition for the PwGDM and PwNGT groups are represented by the average GL for each period (Figure.3). The mean ± standard deviation (SD) GL of the PwGDM and PwNGT groups at the various periods were as follows: period 1, 102.5±27.26 mg/dL and 99.9±22.81 mg/dL; period 2, 115.9±34.15 mg/dL and 105.1±27.27 mg/dL; period 3, 127.9±28.37 mg/dL and 115.4±23.37 mg/dL; period 4, 106.9±15.77 mg/dL and 99.05±14.33 mg/dL, respectively. During labor, the PwGDM and PwNGT groups had similar changes in GL over time. GL peaked in both the PwGDM and PwNGT groups in period 3. A

significant difference was observed in the main effect during the labor period [F(2.12,80.51) = 9.484, P=0.00014], but not for the presence of GDM [F(1,38) = 2.069, P=0.159] or in their interaction [F(2.12,80.51) = 0.512, P=0.612]. During labor, both groups had similar changes in GL over time, which peaked during period 3. Furthermore, differences in GL in the PwGDM group were observed between periods 1 and 2 (P=0.037), 1 and 3 (P=0.024), and 3 and 4 (P=0.005), as well as in the PwNGT group between periods 3 and 4 (P=0.024). For the PwNGT group, a significant difference was observed between periods3 and 4 (P<0.05). However, as ignificant difference was not observed in period4 for both the PwGDM and PwNGT groups (P=0.109) (Figure.3).

Discussion

Hyperglycemia during labor is associated with adverse infant condition ssuch as non-reassuring fetal status, birth asphyxia and neonatal hypoglycemia. Maintaining an appropriate BG level in mothers during labor is associated with the prevention of newborn and infant complications. [18–21] However, no standard strategies for controlling GL during labor have been established. Adequate energy intake for PwGDM during labor plays an important role in avoiding adverse events from glucose metabolism disorders. ACOG recommends that mothers fast during labor, and GL are

then measured after the consumption of glucose during the latent and active labor phases. For a 60-kg pregnant woman, a continuous administration of 1.4–2.1mg/kg/min of 5% intravenous glucose infusion is recommended. [1] In Japan, the strategy used for the control of GL during labor is similar to that stipulated in the ACOG guidelines.[4] However, changes in GL during labor among PwGDM have not been sufficiently investigated. To the best of our knowledge, this study is the first to evaluate the changes in GL during labor among PwGDM and PwNGT.

There sults from this study revealed no significant difference in the average GL among PwGDM and PwNGT between periods 1 to 4. A significant difference was observed in the main effect during the labor period, but not for the presence of GDM. The mother's activity between the active labor phase and period 2 is considered to be strenuous, and energy is expended to maintain this level of intense exercise. Hence, the available glucose must be increased as the body supplies the required amount of glucose during childbirth. [22] However, during the labor period, labor pain makes it difficult for the mother to freely eat or drink. Why did GL increase as parturition neared? Cortisol is a diabetogenic hormone that causes increased GL. Research has shown that pregnant women had high levels of cortisol during the last stage of parturition because it was crucial for fetal respiratory function.[23–25] In this study,

although glucose was not administered continuously, GL gradually increased throughout the delivery, with the average GL peak for both the PwGDM and PwNGT groups occurring in period 3 directly after parturition. Although levels of cortisol were not determined in this study, from the above explanation, it was considered that cortisol levels may explain the increase in GL from parturition until postpartum. The glucose concentrations of PwGDM and PwNGT decreased gradually as they moved towards period 4. In this study, a significant difference was observed in GL between time periods 3 and 4 in both PwNGT and PwGDM groups. Pathologically, the required insulin level for PwGDM should rapidly decrease directly after the placental expulsion, at least to the amount that was required before pregnancy.[26, 27] The decrease in the average GL in the transition period between time periods 3 and 4 for PwGDM and PwNGT was so profound that it resulted in a significant difference. In contrast, the decrease was less for PwGDM. In the very early stages of the postpartum period (directly after and up until 48h after parturition), other factors may cause increase in GL among PwGDM, including insulin resistance caused by pregnancy. Moreover, in mouse experiments, oxytocin was shown to be involved in gluconeogenesis.[28] It is becoming clear that oxytocin regulates glucose metabolism in the body,[29] perhaps through a mechanism that leads to some blood sugar

stabilization. Further studies are needed to clarify the factors affecting glucose kinetics during labor.

From this study, it was found that PwGDM cases can be managed using the same management as for PwNGT cases, because the presence or absence of GDM did not affect GL. Furthermore, it was found that with the increase in GL, there was no influence on perinatal and neonatal prognosis, due to the time period. According toMaritza et al., these data suggest that apolicy for routine insulin infusion in women with GDM, or in women with GDM prescribed with insulin, is not necessary. Furthermore, the use of a dextrose/ insulin infusion during labor and prior to delivery was not associated with a lower risk of neonatal hypoglycemia. When maternal GL were examined, we also did not find that infusions modified the risk of neonatal hypoglycemia.[30] Thus, these CGM-based findings of glucose kinetics during labor may provide the basis for reviewing and revising the current management methods that may be required for expectant mothers.

Our study was subject to some limitations. The number of patients was relatively small, and the investigation was performed at a single facility. Thus, selection bias may have occurred. Furthermore, a comparative study was not carried out between groups allowed to freely eat or drink or those under the current management system

involving fasting and intravenous infusion. In addition, in this study, all women with GDM did not receive insulin treatment between the active labor phase and postpartum. Women with GDM requiring insulin might be treated with a different protocol during delivery.

Further multicentered prospective studies involving more patients would provide more definitive data to clarify the significance of our findings.

Inconclusion, we clarified glucose kinetics during labor for both PwGDM and PwNGT. Interestingly, during labor, both the PwGDM and PwNGT groups showed similar changes in GL over time. GL peaked in period 3 directly after parturition in both the PwGDM and PwNGT groups. During delivery, PwGDM who regularly measured their own GL could be managed using the same nutritional management methods as those for PwNGT.

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Disclosure

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Figure legends

Figure 1. Study enrollment flow chart of pregnant women with gestational diabetes mellitus and normal glucose tolerance.

PwGDM: Pregnant women with gestational diabetes mellitus during labor; PwNGT: pregnant women with normal glucose tolerance

Figure 2. Continuous glucose monitoring levels during labor for one pregnant woman with gestational diabetes mellitus.

PwGDM: Pregnant women with gestational diabetes mellitus, GL: Glucose Levels, SG: Sensor glucose, BG: blood glucose, GDM: gestational diabetes mellitus, SMBG: self-monitoring of blood glucose,

Figure 3. Assessment of glucose kinetics via real-time continuous glucose monitoring during labor for 18 pregnant women with gestational diabetes mellitus and 22 pregnant women with normal glucose tolerance at four time points. Mean: 95% CI; main effect:

period F(2.12,80.51)=9.484; P=0.00014; main effect: DMF(1,38) = 2.069, P=0.159. CI, confidence interval; PwGDM, pregnant women with gestational diabetes mellitus; PwNGT, pregnant women with normal glucose tolerance; SG, sensor glucose.

Supporting information legends

Supporting Document 1. Document specifying that statistical analyses in the present manuscript have been reviewed and revised, if necessary, by a professional data scientist with a doctorate in statistical science in StaGen Co. LTD.

Supporting Document 2. Certification showing that the present manuscript has been edited by a professional English language editing service.