Measuring glucose exposure and variability using continuous glucose monitoring in normal and abnormal glucose metabolism in pregnancy

Roger Mazze1, Yariv Yogev2 & Oded Langer3

1WHO Collaborating Center, International Diabetes Center and Mayo Clinic, Minneapolis, MN, USA, 2Helen Schneider Hospital for Women, Rabin Medical Center, Tel Aviv, Israel, and 3Department of Obstetrics and Gynecology, St. Luke’s Roosevelt Hospital Center, New York, NY, USA

In pregnancy complicated by diabetes periods of hyperglycemia lead to accelerated fetal growth, resulting in a large for gestational age (LGA), or macrosomic, infant. Consequently, our aim was to measure the average volatility or variability in glucose control in women with and without diabetes in pregnancy. Methods: Continuous glucose monitoring (CGM) was employed in 82 pregnant study subjects to collect and record unbiased self-monitored glucose values. We obtained results from 51 women with normal glucose tolerance in pregnancy (NGPT), 25 gestational diabetes (GDM) and 6 women with pregestational diabetes (PreGD) between 18 and 45 (32 ± 6) years of age. Results: Significant differences (p < 0.001) were found in glucose exposure between NGT and all but PreGD; whereas the percent of time in hypoglycemia was significantly (p < 0.0001) higher in all pregnancy groups when compared to the nonpregnant sample. We conclude that CGM confirmed that diurnal glucose patterns differ throughout the day by 20% when pregnant and nonpregnant states are compared. Indeed, maintenance of a narrow range in pregnancy is characteristic in women without diabetes, and CGM throughout pregnancy is critical, if mimicking normal glucose patterns is to be achieved.

Keywords: CGM, gestational glycemia, glycemic profile, perinatal outcomes, stability

Introduction

Pregnancies characterized by normal glucose metabolism have the lowest risk of maternal and fetal complications when compared to those complicated by any degree of dysglycemia. Even near normal glucose values in pregnancy may impart an increased risk of fetal and maternal complications. Women with normal glucose tolerance in pregnancy (NGPT) are characterized by blood glucose levels (60–120 mg/dL or 3.3–6.7 mmol/L) 20% below those of nonpregnant women, and this disparity is maintained throughout pregnancy despite a rise in human placental lactogen, consequential insulin resistance, increased maternal weight and significant changes in diet and activity [1].

These metabolic changes, culminating at the end of pregnancy, are essential for normal fetal nourishment, growth and development and adequate maternal metabolism [2]. Tight glycemic control is not limited to pregnancy; in the nonpregnant state, it has been found that a “narrow range” in blood glucose between 70–140 mg/dL (3.9–7.8 mmol/L) with 50% of the values between 85 and 115 mg/dL (4.7–6.4 mmol/L) is maintained in individuals with normal glucose metabolism, leading one researcher to conclude that, “if the human body spends so much energy to maintain the blood glucose level within such a narrow range, it is because otherwise it would be deleterious” [3,4].

In pregnancy any period of hyperglycemia may lead to accelerated and exaggerated fetal growth, resulting in large for gestational age (LGA), or macrosomic, infants. On the other hand, excessively low blood glucose (hypoglycemia) may retard growth. Variable levels alternating between hyper- and hypoglycemia may have consequences as yet unknown. As expected, such metabolic changes are amplified in pregnancies complicated by diabetes, placing these women at risk for adverse perinatal outcomes [5].

Maintenance of glycemic control in both normal and metabolically challenged pregnancies contributes significantly to the reduction of these adverse perinatal outcomes [6–8]. Consequently, it has become increasingly important to measure the volatility or variability in glucose excursions. There is mounting evidence that glucose instability initiates a cascade of events that lead to acute vascular complications. It is believed that abrupt changes in glucose levels are associated with oxidative stress, which is linked to inflammatory cytokine induction. The path from hyperglycemia and glucose variability to cellular damage begins with the hyper-production of reactive oxygen species (ROS), which leads to cellular damage; notably high concentrations of glucose produce “significant endothelial dysfunction” [3,4].

When these high levels of glucose are subjected to variability beyond very narrow ranges (30 mg/dL or 1.7 mmol/L), the dysfunction worsens. This condition is exaggerated in individuals with diabetes. The notion that abnormal glucose variability during pregnancy may lead to irreparable cellular damage with consequences for both the mother and developing fetus suggests that avoiding glucose oscillations is prudent. Although the consequences for the developing fetus are as yet unknown, the preponderance of evidence supports achieving diurnal glucose profiles within a very narrow range in pregnancy [1,7,8].

Until recently, it has been difficult, if not impossible, to measure the diurnal glucose patterns of women during pregnancy without confining them to bed rest. However, with the advent of continuous glucose monitoring (CGM), it now is feasible to characterize
diurnal glucose patterns to detect the slightest abnormalities in glucose metabolism under usual ambulatory conditions.

In the current study, we set out to employ a novel graphical and statistical analytical program ambulatory glucose profile, in conjunction with CGM, to characterize the diurnal glucose patterns of women with normal glucose metabolism in pregnancy, GDM and gestational diabetes (PreGD) in order to establish references for research and care. Since glycemic control is used as a measure to convey perinatal risk, we felt that an appropriate depiction of both normal and abnormal glycemic control is necessary.

Methods

Ninety-six pregnant women were recruited in this prospective, observational study. Subjects’ glycemic control was assessed by a 100 g oral glucose tolerance test (OGTT) (F > 95, >180, >155 and >140 mg/dL or 5.3, 10, 8.6, 7.8 mmol/L) or by taking a medical history. Subjects were classified as having NGTP, incident gestational diabetes (GDM), or PreGD. For the purposes of comparison, nonpregnant women with normal glucose tolerance (NGT), assembled as historical controls, were added in order to compare reference values with women in the nonpregnant state. Following institutional review board approval, pregnant women presenting sequentially to the clinic for prenatal care were given informed consent to participate in an observational study during which time they would wear a CGM sensor – Medtronic CGMS Guardian (Northridge, CA) – for periods of at least 3 days during their third trimester of pregnancy. Each woman had a sensor placed in the abdominal region, which was attached to a transmitter. The transmitter sent an electronic signal, which was recorded in the CGMS receiver. At the completion of each 3-day cycle, the sensor was replaced. At 12 h intervals or shorter, the sensor was calibrated using self-monitored of blood glucose to account for value differences and time lag between glucose in blood and interstitial fluid. At the completion of the monitoring period, the data were uploaded to a proprietary software program that stored and organized the data according to date, time and value. These data were then transferred to the ambulatory glucose profile (AGP) software for analysis.

AGP treats all CGM values as if they were collected on a single or modal day and plots them according to time without regard to date [9,10]. The AGP consists of five time series, smoothed curves that represent the 10th, 25th, 50th (median), 75th and 90th frequency percentiles (Figure 1). This method is employed to account for repeated glucose measures, which are not subject to a normal distribution. Each AGP report contains summary statistics, including the percent, duration and magnitude of outlier values (i.e. hypo- and hyperglycemic events as defined by user), thereby, visually and statistically portraying overall diurnal glucose characteristics. These characteristics are categorized as glucose exposure, variability and stability to represent the myriad perturbations of glucose metabolism.

AGPs, which can be produced for any number of days, measure overall and periodic glucose exposure by area under the median curve (AUC). Since glucose values determined at the same time each day do not fit a Gaussian distribution, the interquartile range (IQR) is used to represent glucose variability. Therefore, variability is measured as the average difference between the 25th and 75th percentile values for the period under investigation. Glucose stability is expressed as the average absolute hourly rate of change in the median (50th percentile) curve (mg/dL/h) for the entire period. By measuring the changes in the median curve, it is possible to gauge the magnitude of repeated glucose excursions.

Student’s t-test for unequal variance was employed to determine whether there was a significant difference between each subgroup for glucose exposure, glucose variability and the percent of time spent in hypoglycemia. Hypoglycemia was defined for pregnancy as CGM <60 mg/dL (3.3 mmol/L) and for nonpregnancy as CGM <70 mg/dL (3.9 mmol/L).

Results

Eighty-two evaluable women with an average age of 32 ± 6 years completed the study (51 NGTP, 25 GDM and 6 PreGD). GDM patients were either treated with glyburide (15), insulin (3), or diet alone (7). For the purposes of analysis, GDM patients were reclassified as either treated with a therapeutic agent (18) or by diet alone (7). An additional 21 nonpregnant women (31 ± 7 years of age) with NGT were included (Table I). All women

Figure 1. Ambulatory glucose profile reference for normal non-pregnant individuals. In this normal non-pregnant metabolic state, the target glucose range is 70-140 mg/dL (3.9-7.8 mmol/L). Ninety-eight percent of this individual’s recordings fell within this range with a glucose of 97 ± 14 mg/dL (5.4 ± 0.8 mmol/L). The glucose exposure, represented as area under the median curve (AUC), was 2285 mg/dL/24hrs (127 mmol/L/24hrs). The variability (IQR) and stability were 17 mg/dL (0.9 mmol/L) and 1.3 mg/dL/hr (0.07 mmol/L/hr), respectively. Hypoglycemic episodes (<70 mg/dL or <3.9 mmol/L) occurred 0.7 times per day; lasting an average of 30 minutes and accounting for 1.5% of all CGM values.

Figure 2. Ambulatory glucose profile of reference for normal glucose metabolism under usual ambulatory conditions. In the current study, we set out to employ a novel graphical and statistical analytical program ambulatory glucose profile, in conjunction with CGM, to characterize the diurnal glucose patterns of women with normal glucose metabolism in pregnancy, GDM and gestational diabetes (PreGD) in order to establish references for research and care. Since glycemic control is used as a measure to convey perinatal risk, we felt that an appropriate depiction of both normal and abnormal glycemic control is necessary.
Glucose exposure and variability

With abnormal glucose tolerance were treated to 80% of values between 60–120 mg/dL (3.3–6.7 mmol/L). The mean glucose values for glucose exposure, variability and percent hypoglycemia are reported by subgroup in Table II.

The subject from each subgroup whose AGP values most closely resembled the subgroup means was selected as the reference case and is shown in Figures 1–5. Note that the 20% difference in glucose exposure, reported in Table II, between NGT (Figure 1) and NGTP (Figure 2) is characterized by a consistently lower exposure throughout the day and overnight. Additionally, despite differences in appetite, activity and meal timing between nonpregnant and pregnant women, the curves appear almost flat. When all subjects comprising these two subgroups were considered, a significantly higher glucose exposure (p < 0.001) was found for NGT, with no differences in variability and stability. Further comparison between the two subgroups (and illustrated in the figures) revealed a significant difference in the percentage of time spent in hypoglycemia (p < 0.0001).

As reflected in Table II, the reference cases for GDM (shown in Figures 3 and 4), have a lower exposure to glucose than NGT. When all subjects in NGT were compared with the two treatment groups for GDM, we found that GDM was significantly (p < 0.03, therapeutic group and p < 0.001, diet group) lower. As shown in Figures 3 and 4, the characteristically flat and tight AGP for NGTP is not found in the reference case for women treated to target with diet alone or by hypoglycemic agent. In contrast, there was no difference between NGT and women with PreGD in terms of glucose exposure. However, there was significantly (p < 0.0001) higher variability in GDM and PreGD compared to those with NGT or NGTP.

Table I. Maternal demographics by subgroup assignment.

<table>
<thead>
<tr>
<th>Subgroup Assignment</th>
<th>Count (n)</th>
<th>BMI (kg/m²)</th>
<th>Age (years)</th>
<th>Postpartum weight (lbs.)</th>
<th>Gestational age at delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-pregnant (NGT)</td>
<td>21</td>
<td>26 ± 6</td>
<td>31 ± 7</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Normal pregnant (NGTP)</td>
<td>51</td>
<td>26 ± 7</td>
<td>33 ± 2</td>
<td>156 ± 43</td>
<td>39 ± 2</td>
</tr>
<tr>
<td>Gestational diabetes (treated medically)</td>
<td>18</td>
<td>33 ± 7</td>
<td>33 ± 3</td>
<td>188 ± 37</td>
<td>37 ± 2</td>
</tr>
<tr>
<td>Gestational diabetes (diet treated)</td>
<td>7</td>
<td>22 ± 4</td>
<td>38 ± 2</td>
<td>141 ± 26</td>
<td>38 ± 3</td>
</tr>
<tr>
<td>Gestational diabetes (PreGD)</td>
<td>6</td>
<td>32 ± 8</td>
<td>32 ± 6</td>
<td>166 ± 79</td>
<td>38 ± 2</td>
</tr>
</tbody>
</table>

Mean ± SD
BMI, body mass index.

Table II. Analysis of glycemic profile by subgroup assignment.

<table>
<thead>
<tr>
<th>Group (count)</th>
<th>Exposure AUC (mg/dL/24 h)</th>
<th>Variability IQR (mg/dL)</th>
<th>% Hypoglycemia BG &lt; 60 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-pregnant (NGT 21)</td>
<td>2444 ± 165</td>
<td>21.6 ± 4</td>
<td>1 ± 1</td>
</tr>
<tr>
<td>Normal pregnant (NGTP 51)</td>
<td>2042 ± 295</td>
<td>23 ± 9</td>
<td>13 ± 15</td>
</tr>
<tr>
<td>Gestational Diabetes (GDM 24)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated medically (18)</td>
<td>2284 ± 261</td>
<td>35 ± 12</td>
<td>12 ± 11</td>
</tr>
<tr>
<td>Diet treatment (7)</td>
<td>2125 ± 110</td>
<td>27 ± 7</td>
<td>10 ± 5</td>
</tr>
<tr>
<td>PreGestational Diabetes (PreGD 6)</td>
<td>2580 ± 526</td>
<td>50 ± 19</td>
<td>11 ± 7</td>
</tr>
</tbody>
</table>

Mean ± SD
AUC, area under the median curve; IQR, interquartile range.

Figure 3. Ambulatory glucose profile reference for individual with gestational diabetes treated by diet. Seventy-five percent of this individual's recordings fell within range, mean glucose was 93 ± 29 mg/dL (5.2 ± 1.6 mmol/L). Glucose exposure was 2211 mg/dL/24hrs or 123 ± 1.6 mmol/L/24hrs; variability was 35 mg/dL (2 mmol/L) and stability was 7 mg/dL/hr (0.4 mmol/L/hr). Hypoglycemic episodes occurred multiple times (mainly early morning and early evening) lasting an average of 36 minutes and accounting for 10% of all readings.

Figure 4. Ambulatory glucose profile reference for individual with gestational diabetes treated by Glyburide. Seventy-four percent of this individual's recordings fell within range. The mean glucose was (101 ± 27 mg/dL or 5.6 ± 1.5 mmol/L) with glucose exposure, 2421 mg/dL/24hrs (134 mmol/L/24hrs), variability, 34 mg/dL (1.9 mmol/L) and stability 9 mg/dL/hr (0.5 mmol/L/hr). Hypoglycemic episodes occurred twice each day lasting an average of 36 minutes or 4% of all glucose measures.

Figure 5. Ambulatory glucose profile reference for individual with pregestational diabetes (Type 1 Diabetes). Forty-five percent of this individual's recordings fell within range, glucose. Mean glucose was 111 ± 47 mg/dL (6.2 ± 2.5 mmol/L), glucose exposure, 2556 mg/dL/24hrs (142 mmol/L/24hrs); variability, 62 mg/dL (3.4 mmol/L) and stability 7 mg/dL/hr (0.4 mmol/L/hr). The high glucose variability was noted in the wide spread between second and fourth curves or inter-quartile range. It was also noted that 15% of the monitoring was characterized by hypoglycemia (overnight and late afternoon) with episodes occurring at the rate of 4 times per day each lasting an average of 60 minutes.
The average percent of time spent in hypoglycemia was significantly $(p < 0.0005)$ higher in all pregnancy groups when compared to the nonpregnant sample. Among subjects with GDM, there was no significant difference in the percent of hypoglycemia when women treated with diet only were compared with those treated with insulin or glyburide.

**Conclusions**

The physiological importance of tight glycemic control in minimizing perinatal complications is well documented [11]. In the past, in both nonpregnant and pregnant states, glycemic control has been assessed by achieving established HbA$_1c$ levels [12–14]. In normal pregnancies, tight glycemic control has been characterized as an HbA$_1c$ level lower than that of a normal nonpregnant individual with tight glycemic control [15,16]. In diabetic mothers failing to achieve tight glycemic control, the incidence of LGA and macrosomia increase the risk of multiple morbilities, such as cesarean delivery, shoulder dystocia, fetal malformations, neonatal hypoglycemia, jaundice and stillbirth [17].

The American Diabetes Association (ADA) advises pregnancies complicated by PreGD to achieve HbA$_1c$ levels lower than 6% prior to pregnancy in order to attain perinatal risk levels comparable to normal pregnancies [18]. In addition to optimal HbA$_1c$ levels, target pre- and postprandial glucose levels are recommended by the ADA in all pregnancies complicated by diabetes to bestow similar perinatal risk as normal pregnancies. Although HbA$_1c$ is not utilized in GDM, it is assumed that the same metabolic goals are applicable.

Although determining an individual’s HbA$_1c$ level may be an applicable method of estimating gross glucose levels (e.g. mean glucose level of past 3 months), it does not present a measure of daily glucose variability. For instance, employing CGM in pregnancies complicated by diabetes found significant differences in euglycemia, hyperglycemia and hypoglycemia between individuals of similar HbA$_1c$ levels [19,20].

Recently, in a hospital-based cohort of approximately 8000 pregnant women, normal fasting glucose levels throughout pregnancy were characterized with mean, median and interquartile range values [21]. Specifically, mean levels at 4–9 weeks, 10–14 weeks, 15–29 weeks, and in the last 10 weeks of pregnancy were 80 mg/dL, 78 mg/dL, 77 mg/dL and 76 mg/dL (between 4.3 and 4.4 mmol/L) respectively. Similarly, postprandial glucose levels were confirmed to be at least 20% lower than in nonpregnant women with normal glucose metabolism [22–24]. The establishment of normal gestational glucose parameters provides a reference with which to compare pregnancies complicated by diabetes.

Since normal diurnal glucose patterns in pregnancy reduce the risk of complications, it follows that mimicking these patterns in pregnancies complicated by dysglycemia is the appropriate goal for management. Therefore, CGM will be needed as a means of collecting verified, uninterrupted data. With AGP analysis, it will be possible to identify the metabolic defects and select therapies that ameliorate them.

This study had a number of limitations. The technology allowed for only periods of 3-day testing before sensors had to be changed. The women in the study were not randomly selected other than by sequential admission. Measurements of glucose in interstitial fluid (ISF), although accurate and reliable, are not the same as measurements in blood. The time lag and value difference between blood and ISF require careful calibration, which tends to increase in error whenever blood glucose levels are subject to significant change.

Despite these limitations several conclusions may be drawn. First, CGM confirmed that diurnal glucose patterns differ throughout the day by 20% when pregnant and nonpregnant states are compared. Second, maintenance of a narrow range in pregnancy is characteristic of women without diabetes. Third, the many perturbations of glycemic control in women with diabetes (CGM and PreGD) require careful characterization if they are to be ameliorated. Fourth, glucose surveillance throughout pregnancy is a fundamental tool in the management of pregnancy if mimicking normal glycemia is to be achieved.

**Acknowledgements**

The authors wish to acknowledge the contributions of Michael Bancks for his assistance in the preparation of this manuscript. Mr. Bancks worked on the narrative as well as assisted in the statistical analysis. This work was originally presented at the 12th Annual Meeting of the Diabetes in Pregnancy Study Group of North America, 1–2 April 2011, Washington, DC, USA.

**Declaration of Interest:** The authors have no declarations of interest to report.

**References**


*The Journal of Maternal-Fetal and Neonatal Medicine*