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ORIGINAL ARTICLE

Masked hypoglycemia in pregnancy

Highlights
- Glucose dynamics in pregnancy are altered, with a trend towards lower fasting levels in the hypoglycemic range.
- Euglycemic pregnant women, as well as those with gestational diabetes mellitus on insulin, experienced masked hypoglycemia, which may be a physiologic adaptation in pregnancy.
- Hypoglycemic episodes did not adversely affect maternal or fetal outcomes.
- Continuous glucose monitoring uncovered masked hypoglycemia in pregnancy. This was not associated with adverse maternal or fetal outcomes, indicating that low glucose may be a physiologic adaptation.

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Abstract

Background: Hypoglycemia is a major hindrance for optimal glycemic control in women with gestational diabetes mellitus (GDM) on insulin. In the present study, masked hypoglycemia (glucose <2.77mmol/L for ≥30 min) was estimated in pregnant women using a continuous glucose monitoring (CGM) system.

Methods: Twenty pregnant women with GDM on insulin (cases) and 10 age-matched euglycemic pregnant women (controls) between 24 and 36 weeks gestation were recruited. Both groups performed self-monitoring of blood glucose (SMBG) and underwent CGM for 72 h to assess masked hypoglycemia. Masked hypoglycemic episodes were further stratified into two groups based on interstitial glucose (2.28–2.77 and ≤2.22 mmol/L).

Results: Masked hypoglycemia was recorded in 35% (7/20) of cases and 40% (4/10) of controls using CGM, with an average of 1.28 and 1.25 episodes per subject, respectively. Time spent at glucose levels between 2.28 and 2.77 mmol/L did not differ between the two groups (mean 114 vs 90 min; $P = 0.617$), but cases spent a longer time with glucose ≤2.2 mmol/L. Babies born to women with GDM were significantly lighter than those born to controls (2860 vs 3290 g; $P = 0.012$). There was no significant difference in birth weight within the groups among babies born to women with or without hypoglycemia.

Conclusion: Euglycemic pregnant women and those with GDM on insulin had masked hypoglycemia. Masked hypoglycemia was not associated with adverse maternal or fetal outcomes. Therefore, low glucose levels in the hypoglycemic range may represent a physiologic adaptation in pregnancy. This response is exaggerated in women with GDM on insulin.

Keywords: continuous glucose monitoring, gestational diabetes mellitus, masked hypoglycemia.

Introduction

Gestational diabetes mellitus (GDM) is defined as "any degree of glucose intolerance with its onset or first recognition during pregnancy".[1] The prevalence of gestational diabetes ranges from 3.4% to 21% in various parts of India, with a reported prevalence of 16.2% in the south Indian population.[2–4] In pregnancy, maternal blood glucose levels have a continuous relationship with adverse outcomes.[5,6] Uncontrolled hyperglycemia in women with GDM is associated with adverse maternal and perinatal outcomes.[7–9] Optimal glycemic control in women with GDM is essential to prevent these complications, but hypoglycemia is a major hindrance, particularly in those on insulin therapy.[10–12] The current intensive target of fasting glucose levels of 3.33–5 mmol/L may increase the risk of hypoglycemia.[13,14] However, the effect of maternal hypoglycemia on pregnancy outcome is not clear.[15,16]

Hypoglycemia has been found to be more prevalent during pregnancy compared with the non-pregnant state, and occurs in approximately 36%–71% of pregnant women who require insulin.[17,18] In addition, plasma glucose levels during pregnancy are almost 20% lower in normal pregnant women, in GDM, and in pregnant women with pre-existing diabetes compared with non-pregnant women.[19,20] Traditionally, hypoglycemia in pregnancy has been defined as a plasma glucose level <3.33 mmol/L.[21,22] More recently, with the increased availability of continuous glucose monitoring (CGM), the term "masked hypoglycemia" has been introduced. Masked hypoglycemia is defined as interstitial glucose levels <2.7 mmol/L for ≥30 min, without symptoms, detected by CGM.[23,24]

Hypoglycemia during pregnancy can compromise fetal and maternal well being. It has been hypothesized that hypoglycemia during pregnancy can induce potential adverse effects that lead to fetal malformations, small for gestational age and poor neuropsychiatric development.[25–27] The association between the level of hypoglycemia and diabetic embryopathy remains unclear.[28] However, landmark studies on GDM, such as the Hyperglycemia and Adverse Pregnancy Outcome (HAPO)[5] study and the Australian Carbohydrate Intolerance Study (ACHOIS),[6] have not addressed the risk of hypoglycemia and its effect on pregnancy outcomes. The reported incidence of hypoglycemia varies in different studies because hypoglycemia can be asymptomatic, under-recognized, or under-reported.[10–12]

compared with self-monitoring of blood glucose (SMBG) with a glucometer, CGM is superior in determining asymptomatic hypoglycemia, and the results are reproducible and accurate.[29–32] A CGM profile shows the magnitude, duration, and frequency of glucose fluctuations, thereby providing greater insight into the glucose dynamics than intermittent blood glucose measurements with a glucometer.[33]

Hence, the aim of the present study was to objectively estimate masked hypoglycemia in euglycemic pregnant women and those with GDM on insulin therapy using a CGM system.

Methods

The present study was a pilot study. To our knowledge, there are no published studies in the Indian population that have assessed masked hypoglycemia in normal pregnant women and those with GDM. Based on a previously published study,[23] the required sample size with 8% precision error and 80% power to show a significant difference in the duration of hypoglycemia between the two groups was 30 subjects (20 cases and 10 controls).

Pregnant women between 24 and 36 weeks gestation were included in the study. Twenty women aged 18–35 years with GDM (cases) diagnosed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria[34] based on a 75-g oral glucose tolerance test (OGTT) performed between Weeks 24 and 28 of gestation were recruited. Ten age-, body mass index (BMI)-, and gestational week-matched pregnant women with normal glucose levels on the OGTT were selected as controls. Women with pre-GDM and those taking glyburide were excluded from the study. Subjects were recruited between October and December 2013 from the antenatal clinic of the Department of Gynecology and Obstetrics and the GDM clinic of the Department of Endocrinology, Diabetes and Metabolism at Christian Medical College (Vellore, India). All subjects provided written informed consent. This study was approved by the institutional review board (IRB No. 8414; dt.13.08.2013).

Following a diagnosis of GDM, all subjects underwent a 2-week trial of medical nutrition therapy (MNT). Pregnant women who did not achieve adequate glycemic control with MNT (i.e. fasting capillary blood glucose >5.27 mmol/L and/or a 1-h post-meal blood glucose >7.7 mmol/L for 3 consecutive days) were started on insulin, with the dosage titrated to achieve optimal glycemic control. All women with GDM received metformin along with a basal-bolus insulin regimen comprising of thrice daily subcutaneous injections of short-acting human insulin 30 min prior to meals, along with neutral protamine Hagedorn (NPH) once daily before bedtime (usually taken between 2200 and 2230 hours). Blood glucose levels were maintained at a fasting level of <5 mmol/L and 1-h post-meal (i.e. after breakfast, lunch, and dinner) levels of <7.7 mmol/L in

the GDM cases, without any symptomatic hypoglycemia (<3.33 mmol/L). Therapy was adjusted on the basis of SMBG with a glucometer (Bayer Healthcare, Leverkusen, Germany) that uses glucose dehydrogenase enzyme activity. The accuracy of the device, measured by Clarke error grid analysis (EGA),[35] was 88%. Glycemic targets were maintained for at least 3 consecutive days before insertion of a Medtronic Professional CGM device connected to an iPro2 recorder (Medtronic MiniMed, Northridge, CA, USA) on an outpatient basis.

The CGM system measures glucose concentration in the interstitial fluid every 5 min, providing a continuous glucose profile for 72 h comprising of approximately 288 readings during each 24-h period. The Medtronic Professional CGM device has a sensor that is inserted subcutaneously and an iPro2 recorder attached to it. The sensor measures interstitial glucose by converting glucose at a glucose oxidase interface to hydrogen peroxide, which is oxidized to produce an amperometric signal that is recorded. At the end of 72 h, the sensor with the recorder was removed and the amperometric signals stored in the recorder were retrieved by connecting it to a smart dock that uploads data from the iPro2 recorder to the CareLinkiPro software (CGM system solutions version 3.0B; Carelink; Medtronic MiniMed) to provide the interstitial glucose log for 72 h.[36,37]

The CGM sensor was inserted subcutaneously by a trained diabetes nurse educator on Day 1 at the hospital on an outpatient basis. Subjects performed capillary blood glucose measurements using a glucometer (seven times a day: before and 1 h after the three major meals, at bedtime and whenever subjects experienced symptoms of hypoglycemia). Subjects were sent home with the CGM to return after 3 days. Subjects were unaware of the results of the sensor measurements during that period and continued their normal lifestyle as on any other day. The subjects in both groups maintained a diary and recorded the date, time, menu, and quantity of meals and snacks, medication, and all symptomatic hypoglycemic episodes. On Day 3, between 0800 and 0900 hours, subjects returned to the hospital and the sensor with the recorder was removed. The stored amperometric data in the iPro2recorder were downloaded following calibration with the recorded blood glucose values using the CareLink iPro software (CGM system solutions version 3.0B; Carelink; Medtronic MiniMed) and a glucose log report generated.

Masked hypoglycemia was defined as ≥30 min (consecutive) of glucose values ≤2.77mmol/L detected by CGM without symptoms.[23] Further, masked hypoglycemic episodes were stratified into two subgroups: (i) those with glucose values ranging from 2.28 to 2.77 mmol/L; and (ii) those with glucose values ≤2.22 mmol/L (below the reporting limit of the CGM device).

Statistical analyses

Data were entered in Epidata version 3.1 (Epidata Association, Odense, Denmark) and transferred onto an Excel sheet (Microsoft, Bellevue, WA, USA). Statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Independent samples *t*-tests were used to compare the means of two continuous variables. Unless indicated otherwise, data are presented as the mean ± SD. Two-sided $P < 0.05$ was considered significant.

Results

The mean age of the cases and controls was 29.7 ± 4.8 and 28 ± 4.4 years, respectively. The baseline characteristics (age, weight, prepregnancy body mass index, blood glucose levels at diagnosis of GDM and gestational age at CGM) of the cases and controls are listed in Table 1. The glycemic parameters recorded by glucometer showed a mean preprandial glucose level of 4.64 ± 0.96 mmol/L in cases, which was not significantly different from that in the control group (4.41 ± 0.61 mmol/L; $P = 0.14$). However, mean 1-h postprandial blood glucose was significantly higher in women with GDM on insulin than in the controls (7.21 ± 1.52 vs. 5.98 ± 0.82 mmol/L, respectively; $P = 0.01$). Mean midnight glucose levels were similar in the two groups (4.79 ± 0.67 vs 4.82 ± 0.9 mmol/L in cases and controls, respectively; $P = 0.761$). During the study period, none of the subjects in either group had any episode of documented symptomatic hypoglycemia.

The CGM profiles of cases and controls over 72 h are shown in Figs 1 and 2. Masked hypoglycemia was recorded in 35% (7/20) of cases and 40% (4/10) of controls with an average of approximately 1.28 and 1.25 episodes per subject, respectively (Fig. 3). Most (>90%) hypoglycemic events were nocturnal (2300–0600 hours). The mean nocturnal interstitial glucose levels (2300–0600 hours) in cases and controls were 3.16 ± 0.61 and 3.26 ± 0.62 mmol/L, respectively. Further, the average time spent at glucose levels between 2.28 and 2.77 mmol/L did not differ significantly between the two groups (114 vs 90 min in cases and controls, respectively; $P = 0.617$; Fig. 4). However, two cases spent a significantly longer time at glucose levels ≤2.22 mmol/L compared with a single control subject (232 min/case vs 10 min in one control subject; Fig. 4). Interestingly, neither group exhibited a Somogyi phenomenon, even with blood glucose levels ≤2.77 mmol/L.

Pregnancy outcome

Three women with GDM had hypertension. A greater proportion of cases with GDM (45%) underwent

Table 1 Clinical characteristics of cases (women with gestational diabetes on insulin therapy) and controls (women without gestational diabetes)

Clinical characteristics	Cases	Controls	*P*-value
Age (years)			0.33
Mean ± SD	29.8 ± 4.8	28 ± 48	
Median (minimum–maximum)	30 (21–36)	29 (21 34)	
Weight (kg)	69.9 ± 8.8	68.1 ± 10.3	0.63
Height (cm)	155 ± 8	157 ± 5	0.59
Prepregnancy BMI (kg/m^2)	26.8 ± 4.4 (*n* = 14)	26.1 ± 5.6 (*n* = 8)	0.77
Gestational age at CGM (weeks)	30.1 ± 4.5	30 ± 4	0.97
SBP (mmHg)	116 ± 11	103 ± 8	<0.001
DBP (mm Hg)	71.7 ± 7.3	70.8 ± 4.73	0.69
Plasma glucose on 75-g OGTT (mg/dL)			
0 h	122 ± 30 (*n* = 15)	77.3 ± 5.9 (*n* = 10)	<0.001
1 h	242 ± 83 (*n* = 5)	113 ± 23 (*n* = 10)	0.02
2 h	193 ± 86 (*n* = 11)	103 ± 14 (*n* = 10)	0.006

Unless indicated otherwise, data are given as the mean (± SD). *P*-values were determined by independent *t*-tests.
BMI, body mass index; CGM, continuous glucose monitoring; DBP, diastolic blood pressure; OGTT, oral glucose tolerance test; SBP, systolic blood pressure.

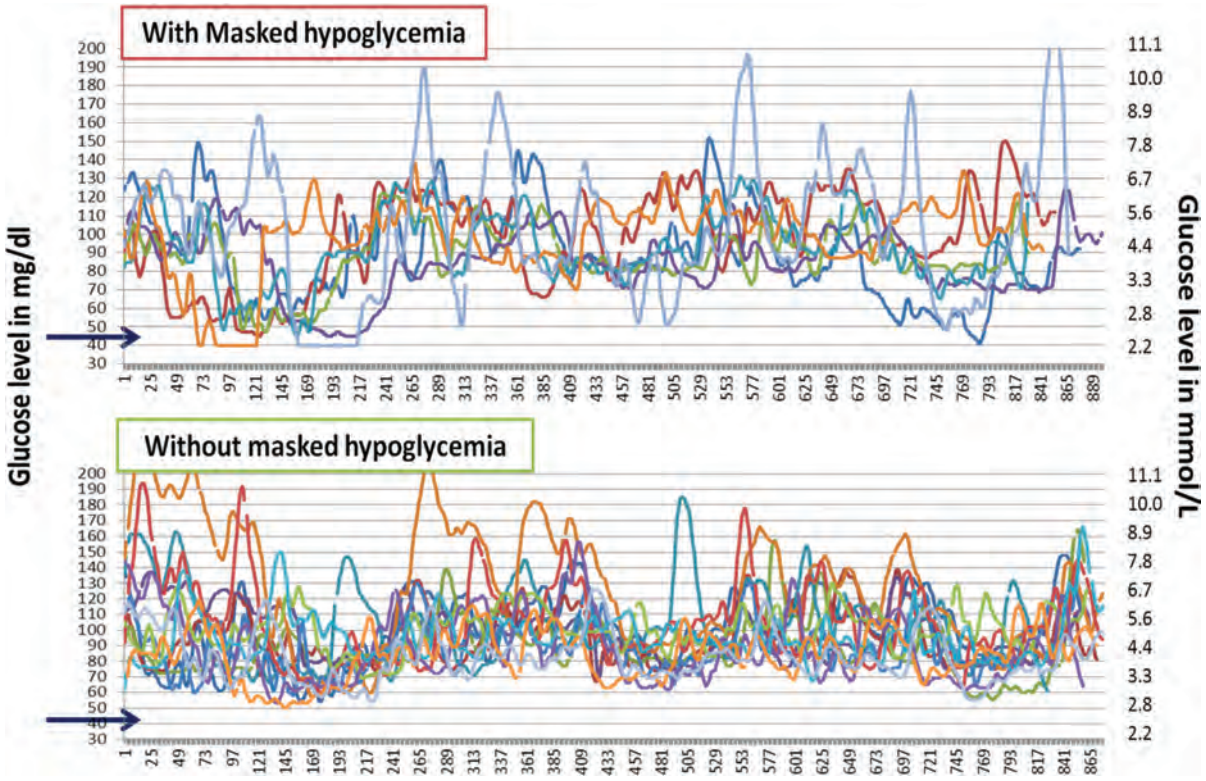

Figure 1 Continuous glucose monitoring profiles in women with gestational diabetes mellitus on insulin (a) with or (b) without masked hypoglycemia. Graphs show glucose profiles in individual women over 72 h. (a) In women with GDM and masked hypoglycemia, the episodes of masked hypoglycemic occurred mostly during the night (2300–0600 h), corresponding to values numbered 124–230, 432–518, and 720–820 (on the first, second and third nights, respectively). (b) In women with GDM but no masked hypoglycemia, there was a trend towards lower glucose values at night (2300–0600 h), corresponding to values numbered 124–230, 432–518, and 720–820, but these values were above 2.77 mmol/L (50 mg/dL).

cesarean section, three on an emergency basis (two due to fetal distress and one due to severe pregnancy-induced hypertension) and six for elective obstetric indications. Only 20% of controls underwent cesarean section. Macrosomia was not noted in any of the babies born to women with GDM.

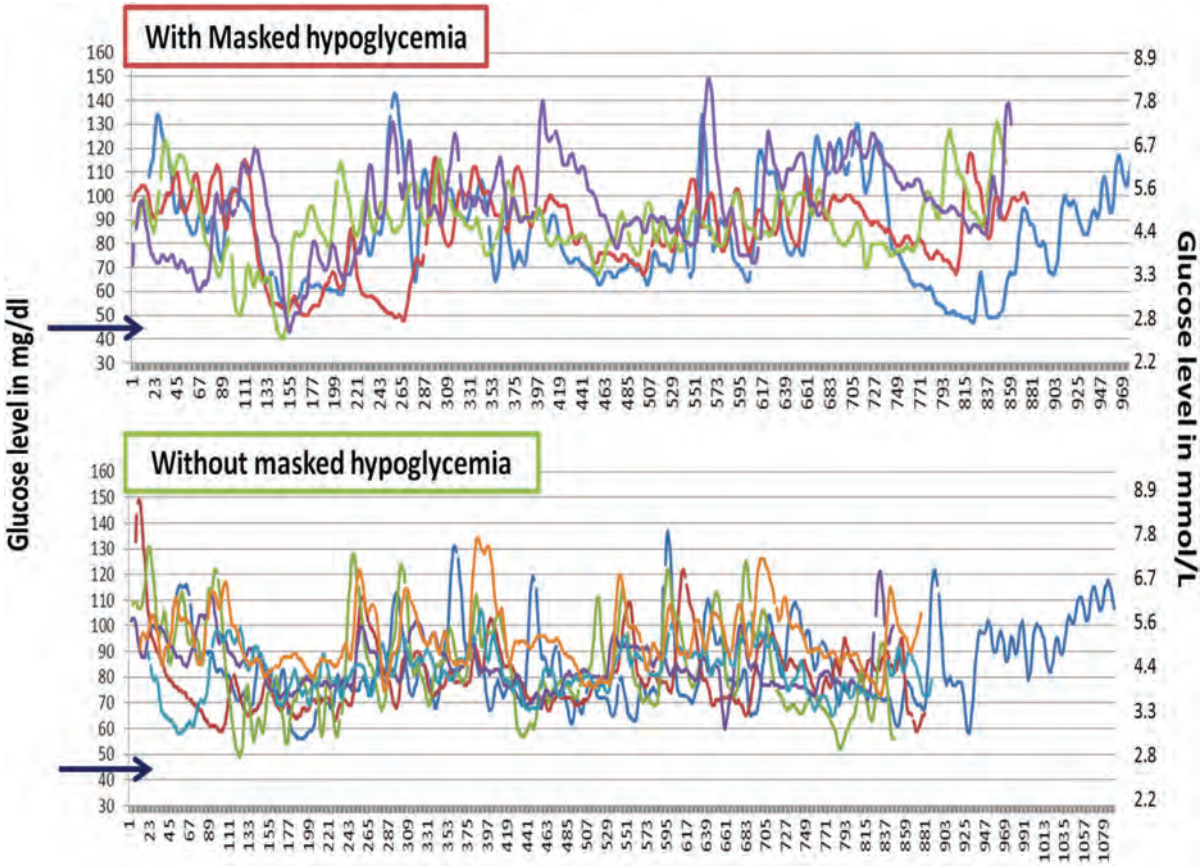

Figure 2 Continuous glucose monitoring profiles in women without gestational diabetes mellitus (a) with or (b) without masked hypoglycemia. Graphs show glucose profiles in individual women over 72 h. (a) In women with masked hypoglycemia, the episodes of masked hypoglycemic occurred mostly during the night (2300–0600 h), corresponding to values numbered 124–230 and 720–837 (on the first and third nights, respectively). (b) In women without masked hypoglycemia, there was a trend towards lower glucose values at night (2300–0600 h), corresponding to values numbered 124–230, 432–518 and 720–820, but the values were above 2.77mmol/L (50 mg/dL).

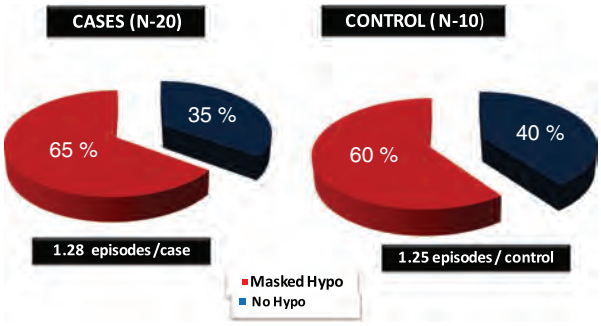

Figure 3 Pie chart showing the distribution of subjects with and without masked hypoglycemia in the cases (women with gestational diabetes mellitus) and controls (women without gestational diabetes mellitus).

Babies born to women with GDM were significantly lighter compared with those born to controls (mean 2860 vs 3290 g, respectively; $P = 0.012$). However, there was no significant difference in birth weight within the groups among babies born to women with or without hypoglycemia.

Discussion

The primary objective of the present study was to detect masked (asymptomatic) hypoglycemia in women with GDM on insulin therapy. Masked hypoglycemia was observed in GDM women treated with insulin, as well as pregnant women without GDM. Most (>90%) hypoglycemic events were nocturnal (2300–0600 hours). Lower nocturnal blood glucose levels were found in the present study compared with previous reports.[30] In another study,[19] obese pregnant women without diabetes had lower nocturnal blood glucose levels than non-obese subjects. Further, Parretti et al. reported an overall daily mean blood glucose concentration of

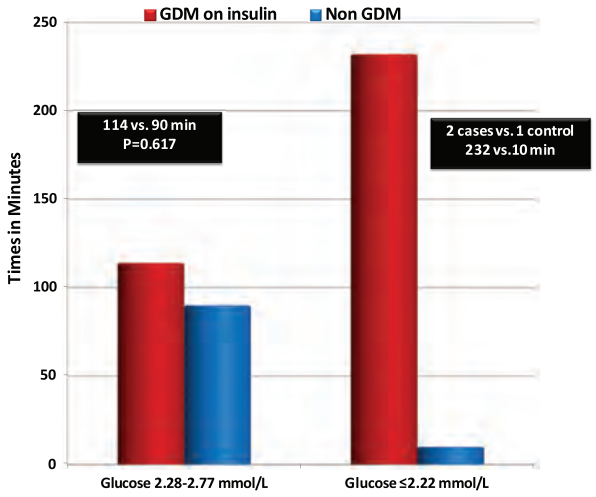

Figure 4 Mean duration of time spent by cases (seven of 20 women with gestational diabetes mellitus) and controls (four of 10 women without gestational diabetes mellitus) in hypoglycemia. The time spent at glucose levels between 2.28 and 2.77 mmol/L per subject did not differ between cases and controls (114 vs 90 min, respectively). Cases spent a significantly longer duration at glucose levels ≤2.22 mmol/L. Specifically, two cases spent a significantly longer time at glucose levels ≤2.22 mmol/L compared with a single control subject (232 min/case vs 10 min in one control subject).

4.12 ± 0.28 mmol/L, with blood glucose concentrations at 2200, 2400 and 0400 hours of 3.46 ± 0.22, 3.57 ± 0.28, and 3.3 ± 0.8 mmol/L in normal pregnant women.[38] The nocturnal hypoglycemia in both groups in the present study could be accounted for, in part, by the persistence of normal circadian rhythms for glucose.[39–41]

In the present study, asymptomatic hypoglycemic episodes were observed not only in women with GDM on insulin, but also in controls. The hypoglycemic episodes were more prolonged in women with GDM on insulin. Masked hypoglycemia was diagnosed as at least 30 min of interstitial glucose (six consecutive values) in the hypoglycemic range below the cut-off value. Hence, we could determine with reasonable certainty that masked hypoglycemic episodes represented true sustained low values. Asymptomatic blood glucose levels <2.77 mmol/L were noted more frequently at night and there were occasional hypoglycemic episodes mid-morning and prior to dinner. None of these hypoglycemic episodes was captured by capillary blood glucose testing. This could be attributable to the timing of testing: most hypoglycemic episodes occurred while the subjects were asleep or during mid-morning when they did not check capillary blood glucose if they were asymptomatic.

In addition, in women with GDM on insulin therapy, 40% had masked hypoglycemia and 10% of these women had glucose levels ≤2.22mmol/L, suggesting a lower threshold for developing hypoglycemia. Continuous glucose monitoring does not measure glucose values below 2.22 mmol/L.[42] A small study in seven well-controlled type 1 diabetes subjects reported poor agreement between CGM values and those measured by a glucose analyzer at values in the hypoglycemic range.[43]

A CGM system is considered a better tool than SMBG in determining masked hypoglycemia in any clinical setting. Other studies have reported reasonable accuracy of CGM in the hypoglycemic range. The absolute relative difference (ARD) for CGM values in the hypoglycemic range (2.22–3.88 mmol/L) was approximately 20%–30%.[44] A study using the iPro algorithm demonstrated that at values ranging from 2.22 to 4.44 mmol/L, 88.7% of adult and 85.5% of pediatric sensor glucose values were within 20 mg/dL of the reference value (from a blood glucose monitor).[45]

The mechanisms of nocturnal hypoglycemia in normal pregnancy have not yet been elucidated. Changes in fuel metabolism in the mother have been proposed as possible mechanisms: insulin resistance leading to increased transplacental transport of glucose to the fetus from mother[46,47] and increased fatty acid metabolism and lipolysis.[48,49] Another mechanism that could explain nocturnal hypoglycemia in normal pregnant women could be related to a lower area under the curve blood for 24-h glucose.[50]

Despite documented low glucose values (≤2.77mmol/L), the Somogyi phenomenon was not observed in either group in the present study. Counter-regulatory glucagon, epinephrine, cortisol, and growth hormone responses to hypoglycemia have been documented to be diminished in women with insulin-requiring diabetes during pregnancy.[51,52] This may be an independent effect of pregnancy itself. The threshold for release of epinephrine and growth hormone in insulin-dependent pregnant women with diabetes was 0.28–0.56 mmol/L lower than in controls.[53] Thus, it may be conjectured that the increased duration of masked hypoglycemia without a Somogyi phenomenon in these subjects may be due, in part, to a reduced counter-regulatory hormonal response. Hypoglycemia was observed in pregnant women without GDM, as well as in those with GDM. This implies that low glucose values may be a physiologic adaptation in pregnancy, which was exaggerated in women with GDM on insulin who experienced a longer duration of hypoglycemia.

Several studies have shown a positive association of higher maternal blood glucose levels with macrosomia and cesarean section in women with diabetes mellitus

complicating pregnancy.[5,54,55] Intensive glycemic control in patients with GDM reduces the risk of cesarean section.[56,57] In the present study, a greater proportion of cases with GDM underwent cesarean section than normoglycemic pregnant women (45% vs 20%, respectively). Two-thirds of the cesarean sections in GDM women were for elective obstetric indications. Hence, they were unlikely to be related to diabetes complicating pregnancy.

Babies born to women with GDM were significantly lighter than those born to controls (2860 vs 3290 g, respectively; $P = 0.012$). A retrospective study by Vadakekut et al. found a lower birth weight for newborns of women with hypoglycemia that those born to women with normal blood glucose levels.[58] There were no differences in pregnancy outcomes or birth weight in cases and controls with or without hypoglycemia (interstitial blood glucose levels <2.77mmol/L) in the present study. Diamond et al. have reported that basal fetal heart rate remains unchanged and continues to manifest accelerations during the hypoglycemic state.[53] No consistent changes in Doppler velocity waveforms were observed during hypoglycemia induced with the insulin clamp technique in diabetic pregnant women and fetal well being remained unaltered despite moderate hypoglycemia in another study.[59]

The present study has several limitations. First, the sample size was small, although it was based on a scientific sample size calculation. However, the basic limitation to attaining a larger sample size was that pregnant women often refused to give informed consent to take part in a study wherein sensors were inserted for continuous monitoring of glucose levels. This was particularly a problem in women who did not have diabetes in pregnancy. Glucose levels were monitored with a glucometer, which may have a lower precision and accuracy than determination of plasma glucose levels. However, it would be impractical to obtain multiple blood samples for plasma glucose testing in pregnant women. Hormonal axes have not been assessed in relation to insulin, glucagon, and C-peptide levels, which could provide further insights into the mechanism of nocturnal dips in glucose in pregnancy. Moreover, we did not study the glucose dynamics in age-matched non-diabetic, non-pregnant women, which would have probably provided useful insights into these mechanisms.

Conclusion

Continuous glucose monitoring is a valuable tool to study altered glucose dynamics in pregnancy. Significant proportions of pregnant women without GDM, as well as those with GDM and on insulin, had masked hypoglycemia. This may represent a physiologic adaptation in pregnancy that is exaggerated in women with GDM on insulin who experience a longer duration of hypoglycemia. In view of nocturnal hypoglycemia, we suggest that pregnant women take adequate bed time snacks to prevent hypoglycemia. The implications of low fasting glucose levels in pregnant women without GDM may need further investigation in a larger population.

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Disclosure

The authors declare no conflicts of interest.

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