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SHORT COMMUNICATION

A. Kerssen · H. W. de Valk · G. H. A. Visser

Do HbA_1c levels and the self-monitoring of blood glucose levels adequately reflect glycaemic control during pregnancy in women with type 1 diabetes mellitus?

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Abstract *Aims/hypothesis:* Pregnancies of women with type 1 diabetes mellitus are associated with maternal and perinatal complications. These complication rates remain elevated despite achievement of the treatment goals described in the widely used guidelines of the American Diabetes Association (i.e. HbA_1c level ≤7.0%). Against this background, we sought to answer two questions: (1) are HbA_1c levels within 1% above normal appropriate in pregnant women with type 1 diabetes or should treatment be aimed at normal HbA_1c levels; and (2) how many self-monitored blood glucose (SMBG) levels are needed per day to obtain an adequate image of glycaemic control in pregnant women with type 1 diabetes? *Materials and methods:* We asked 43 pregnant women with type 1 diabetes to use the Continuous Glucose Monitoring System (CGMS) once in each trimester of pregnancy, while continuing their SMBG measurements. Glucose levels measured with the CGMS were compared between patients with HbA_1c levels of 4.0–6.0%, 6.0–7.0% and >7.0%. Self-monitored glucose levels and those measured with CGMS were compared between patients with four or five, six to nine and ten or more SMBG determinations daily. *Results:* In patients with HbA_1c levels ≤6.0%, the glucose levels obtained by CGMS were significantly better than in patients with HbA_1c levels >6.0%. In women with HbA_1c levels 6.0–7.0% and >7.0%, these levels did not differ. The detection rate of hyper- and hypoglycaemic episodes was significantly higher in patients with ten or more SMBG determinations daily than in patients with fewer than ten. *Conclusions/interpretation:* Treatment of diabetes in pregnant women should be aimed at achieving HbA_1c levels within the normal range, i.e. ≤6.0%. A minimum of ten SMBG determinations daily is necessary to obtain adequate information of all daily glucose fluctuations.

Keywords Continuous Glucose Monitoring System · Glycaemic control · HbA_1c level · Pregnancy · Self-monitoring of blood glucose levels · Type 1 diabetes mellitus

Abbreviations ADA: American Diabetes Association · CGMS: Continuous Glucose Monitoring System · SMBG: self-monitoring of blood glucose levels

Introduction

Pregnancy in women with type 1 diabetes mellitus is associated with an increased incidence of perinatal complications [1]. It is generally accepted that complication rates decrease when glycaemic control during pregnancy is tightened. The widely used guidelines of the American Diabetes Association (ADA) state that in pregnancy HbA_1c levels within 1% above the upper limit of normal range are desirable, as these are assumed to be associated with rates of congenital malformations equal to those in healthy women [2]. However, it has been shown that in patients with these 'acceptable' HbA_1c levels, complication rates remain higher than in patients with normal HbA_1c levels [1, 3]. The most obvious explanation for this finding is that in patients with HbA_1c levels within 1% above normal, glucose levels are not within an acceptable range [4].

Currently, self-monitoring of blood glucose (SMBG) is the established and easiest way of observing daily glucose levels in patients with diabetes. The frequency and timing of SMBG should be dictated by the particular needs and goals of the patients. During pregnancy, SMBG is recommended at least three times per day in women with type 1 diabetes [5]. SMBG, however, has its limitations and with the high

A. Kerssen (✉) · G. H. A. Visser
Department of Perinatology and Gynaecology,
University Medical Centre Utrecht,
KJ.02.507.0/P.O. Box 85090,
3508 AB Utrecht, The Netherlands
e-mail: a.kerssen@umcutrecht.nl
Tel.: +31-30-2504913
Fax: +31-30-2505320

H. W. de Valk
Department of Internal Medicine and Dermatology,
University Medical Centre Utrecht,
Utrecht, The Netherlands

complication rates in pregnancies of women with type 1 diabetes, accurate reflection of glucose levels is important.

The first aim of this study was to evaluate the appropriateness of the limits of HbA_1c levels currently recommended in international guidelines during pregnancy. The second aim was to assess how many SMBG determinations have to be obtained daily to give an accurate idea of glucose levels in pregnant women with type 1 diabetes.

Subjects, materials and methods

The continuous glucose monitoring system

The Continuous Glucose Monitoring System (CGMS) is a portable device (CGMS; MiniMed, Sylmar, CA, USA) that measures glucose levels in the extracellular fluid of the abdominal subcutaneous tissue for an uninterrupted period of up to 72 h. With this device, ambulatory continuous glucose monitoring is possible while patients maintain their usual daily activities. The CGMS stores values within a range of 2.2 to 22.2 mmol/l every 5 min, providing 288 readings in 24 h. The CGMS does not display glucose values and the data saved in the monitor are downloaded and printed after removing the sensor. Patients need to calibrate the system by entering data from at least four fingerstick glucose measurements each day.

The data of the CGMS are considered valid if three criteria for optimal accuracy are met: (1) at least four paired sensor glucose values and meter glucose readings per day; (2) correlation coefficient between sensor glucose values and meter blood glucose readings ≥0.79; and (3) average value of differences between sensor glucose values and meter glucose readings for a given day ≤28% [6]. It has been shown that the CGMS is an accurate tool for glucose monitoring in pregnant women with type 1 diabetes [7]. In the present study glucose profiles measured with the CGMS were used only if the accuracy criteria were met and if none of the 288 glucose measurements per 24 h was missing.

Materials and methods

The study was approved by the ethics committee of the University Medical Centre Utrecht, The Netherlands. From December 2001 through to June 2004, 43 pregnant women with type 1 diabetes were recruited from our obstetrical outpatient clinic. All patients gave written informed consent to participate in the study. The patients were asked to use the CGMS once in each trimester of the pregnancy.

HbA_1c levels were determined within 1 week after each continuous glucose measurement. In 55% of the patients, HbA_1c levels were also obtained 6–8 weeks after the CGMS measurement. Comparison of the two HbA_1c levels showed a correlation coefficient of 0.83 ($p<0.001$). A paired *t*-test showed that HbA_1c levels obtained 1 week or 6–8 weeks after the CGMS measurement were not significantly different. HbA_1c levels determined within 1 week after the CGMS measurement were therefore found fit to use in the present study.

The patients were asked to maintain their regular SMBG schedule on the days the CGMS was used, with a minimum of four SMBG determinations per day—the amount needed for calibration of the CGMS. All SMBG determinations were performed through fingerstick measurement and were determined with the MediSense Precision Xtra glucose meter (Abbott, Bedford, MA, USA).

Analysis

Glucose levels measured with the CGMS were expressed as mean and range per 24 h. Hyperglycaemia was defined as a glucose level ≥7.8 mmol/l and hypoglycaemia was defined as a glucose level ≤3.9 mmol/l. The number of hyper- and hypoglycaemic episodes per 24 h measured with the CGMS were counted. Glucose variability of the glucose levels measured with the CGMS was expressed as the CV (100×SD/mean).

Mean glucose level, glucose range, number of hyper- and hypoglycaemic episodes and CV of the CGMS glucose levels were compared between patients with a normal HbA_1c level (≤6.0%), those with HbA_1c levels within 1% above normal range (6.0–7.0%) and those with 'not optimal' HbA_1c levels (>7.0%) using one-way ANOVA and post hoc Bonferroni.

The measurement days were categorised into three groups: (1) four or five SMBG determinations daily; (2) six to nine daily; and (3) ten or more daily. For each measurement day, the hyper- and hypoglycaemia detection rate was calculated. The hyper- and hypoglycaemia detection rates were compared between the three groups using one-way ANOVA and a post-hoc Bonferroni correction. For evaluation $p<0.05$ was considered significant.

Results

No adverse events were associated with the use of the CGMS. A total of 212 measurement days were obtained, of which 185 days (87%) fulfilled the predefined requirements for analysis. The number of measurement days in the first,

Table 1 Mean glucose level, glucose range, number of hyper- and hypoglycaemic episodes and CV per 24 h of CGMS glucose levels in patients with different HbA_1c levels

	HbA_1c level		
	4.0–6.0%	6.0–7.0%	>7.0%
Mean glucose level (mmol/l)	5.6	7.0	7.8
Glucose range (mmol/l)	6.7	9.6	11.6
Hyperglycaemic episodes (*n*)	2.1	3.4	3.9
Hypoglycaemic episodes (*n*)	3.2	2.3	2.0
CV (%)	27	34	39

Table 2 Mean glucose level, glucose range, number of hyper- and hypoglycaemic episodes per 24 h of SMBG determinations and CGMS glucose levels in patients with different numbers of SMBG determinations

	Number of SMBG determinations					
	4–5		6–9		≥10	
	SMBG	CGMS	SMBG	CGMS	SMBG	CGMS
Mean glucose level (mmol/l)	6.8	6.9	6.5	6.3	6.2	6.3
Glucose range (mmol/l)	5.1	9.6	6.4	8.1	7.8	8.9
Hyperglycaemic episodes (*n*)	1.2	3.4	1.7	2.9	1.8	1.8
Hypoglycaemic episodes (*n*)	0.6	2.3	1.2	2.5	2.7	3.7

second and third trimester of pregnancy was 68, 59 and 58, respectively. HbA_1c levels ranged from 5.1 to 9.1%. The HbA_1c level was ≤6.0% in 58 (31%), 6.0–7.0% in 104 (56%) and >7.0% in 23 (12%) of the measurement days.

The HbA_1c levels and CGMS glucose values are shown in Table 1. In patients with HbA_1c levels ≤6.0% all but one of the glucose measures were significantly better ($p<0.001$) than in patients with HbA_1c levels of 6.0–7.0% or >7.0%. Only the number of hypoglycaemic episodes was significantly higher ($p<0.05$). Glucose measures in women with HbA_1c levels 6.0–7.0% and >7.0% did not differ significantly, apart from mean glucose and glucose range ($p<0.05$).

SMBG determinations were performed four or five, six to nine and ten or more times per day on 92, 70 and 23 days, respectively. Mean HbA_1c levels did not differ significantly between the groups (6.5, 6.3 and 6.2%, respectively), nor did the mean glucose values (Table 2). The mean glucose level, glucose range and number of hyper- and hypoglycaemic episodes measured with SMBG and the CGMS are given in Table 2. Hyperglycaemia detection rates increased significantly ($p<0.05$) with an increase in the number of SMBG determinations (35, 59 and 100%, respectively). Hypoglycaemia detection rate was significantly higher in the third group (73%) than in the first (26%, $p<0.01$) and second (48%, $p<0.05$).

Discussion

This study shows that there is a significant difference in glycaemic control between patients with HbA_1c levels within the normal range (≤6.0%) and patients with HbA_1c levels above the normal range (>6.0%). No difference in glycaemic control was seen between patients with 'acceptable' HbA_1c levels (6.0–7.0%) and those with 'not optimal' HbA_1c levels (>7.0%). These results conflict with the guidelines of the ADA, which state that in pregnancy HbA_1c levels ≤7.0% are acceptable [2]. This study also shows that hyper- and hypoglycaemia detection rates increase when patients measure their blood glucose levels ten or more times daily. The hyperglycaemia detection rate rises to 100%. The detection rate of hypoglycaemic episodes, however, did not exceed 73%. It is unlikely that biochemical detection of hypoglycaemic episodes will ever be 100% as these often occur in the night and early morning hours when patients are sleeping [8].

Our findings indicate that the current guidelines might not be accurate. However, before changing guidelines or clinical practice, further research should be performed evaluating the effects of the normalisation of HbA_1c levels and of a more frequent performance of SMBG determinations on pregnancy outcome. Also the risk of normalising HbA_1c levels should be assessed. Normalisation of blood glucose levels in pregnant women with diabetes is associated with an increased risk of hypoglycaemic episodes [9]. This finding is confirmed in the present study, as the number of hypoglycaemic episodes increased when HbA_1c levels were ≤6.0%. Thirdly, we should ask ourselves whether, with the currently available insulins and procedures, we are able to treat all glucose fluctuations that are measured. In a previous study we have shown that treatment adjustments are difficult to make in women whose diurnal glucose profiles show large fluctuations [10]. In some women, glucose fluctuations will persist despite the extreme efforts of both doctors and patients. Finally, the usefulness of HbA_1c levels as a measure of glycaemic control in pregnant women with diabetes should be reassessed. Even in women with normal HbA_1c levels, hyper- and hypoglycaemic episodes were present. Is it a too gross measure of glycaemic control or are there other, for example, genetic or familial factors that cause the gap between actual glucose levels and HbA_1c levels?

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