Increased second trimester maternal glucose levels are related to extreme large-for-gestational age infants in women with type 1 diabetes mellitus

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ABSTRACT

Objective Large-for-gestational age infants (LGA, birth weight ≥90th centile) are a continuing problem in pregnancies of women with type 1 diabetes. We used a continuous glucose monitoring system (CGMS) to assess the relationship between 24-hour diurnal glucose profiles in all three trimesters of the pregnancy and infant birth weight.

Research Design and Methods Twenty-nine pregnant women with diabetes used the CGMS during each trimester of pregnancy. The glucose profiles of the women with a normal weight infant or a LGA infant were compared.

Results 48% of the women with diabetes gave birth to a LGA infant. 50% of these infants were already large-for-dates on ultrasound <30 weeks of gestation (early LGA) and all these infants had a birth weight ≥97.7th centile. The diurnal glucose profiles show that the mothers of early LGA infants had elevated glucose levels for most of the day during the second trimester (p<0.05). The median 24-hour glucose level was significantly higher in women who gave birth to early LGA infants in all three trimesters of pregnancy (6.7, 8.3, 6.5 mmol/l, respectively). Within the group of women with early LGA infants the second trimester median glucose level was significantly higher than that in the first and third trimester (p<0.05).

Conclusions In women with type 1 diabetes extreme growth of the fetus starts early in pregnancy and this is likely to be caused by increased maternal glucose levels. Further investigation is needed to see whether early tight glycaemic control will reduce the number of extreme LGA infants.
Treatment of pregnant women with type 1 diabetes mellitus is aimed at achieving a pregnancy outcome that approximates that of non-diabetic women (1). Recent studies have shown that this target is far from being reached despite modern methods of treatment (2-6) and despite the maintenance of HbA1c-levels within the limits advised in international guidelines (2, 7).

Large-for-gestational age infants (birth weight ≥90th centile) are the most frequent of the complications seen in pregnancies of women with type 1 diabetes (2-6, 8, 9). It is associated with increased morbidity of both mother and child (10-12). It has been shown that the large-for-gestational age infant rate is positively related to glycaemic control (13-16). Discrepancy, however, exists concerning the trimester of pregnancy in which tight glucose regulation is considered the most important. Page et al. conclude that the incidence of macrosomia may be reduced by tighter control of diabetes at conception and during the first trimester (14) while two others studies show that second and third trimester glucose values are related to neonatal morbidity (13, 15). A more recent study has shown that only second trimester glucose levels are related to perinatal outcome (16). An obstacle in the existing studies is that glycaemic control was expressed as the mean of six to eight self-monitored blood glucose levels a day. It is not likely that the mean of six to eight self-monitored glucose levels a day truly reflects the diurnal glucose profile (17). A novel method for the continuous monitoring of glycaemic control is the Continuous Glucose Monitoring System (CGMS, MiniMed, Sylmar, CA 91342, USA). This device measures glucose levels in the extracellular fluid of the abdominal subcutaneous tissue and stores values in a range of 2.2-22.2 mmol/l every 5 minutes for a maximum of 72 hours. Besides interstitial glucose levels, the monitor stores event markers for meals, insulin injections and exercise. For the calibration of the system, finger stick blood glucose levels need to be entered into the system. The data from the CGMS are, according to the MiniMed instructions, valid if three criteria for optimal accuracy are met: 1) At least four paired sensor glucose / meter glucose readings per 24 hours. 2) Correlation coefficient between sensor glucose values and these four meter blood glucose readings ≥ 0.79. 3) Average value of differences between sensor glucose values and meter glucose values for a given day ≤ 28% (18).

In this 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 hours were missing. The first 24 hours of each CGMS measurement that best met the manufacturer’s accuracy criteria were used for the main analyses. In a previous study we have shown that as many as 45% of the pregnant women with type 1 diabetes have wide day-to-day fluctuations in multiple-day CGMS measurements (19). To observe the possible effects of these day-to-day fluctuations on the results and conclusions of the present study, we repeated the analyses on the data of the day of the CGMS measurement that second-best met the manufacturer’s accuracy criteria, in those
cases with at least 48 hours of recording of sufficient quality.

**Patients and Methods**

The study was approved by the ethics committee of the University Medical Centre Utrecht, The Netherlands and all subjects gave written informed consent before entering the study.

From December 2001 through June 2004 fifty-one pregnant women with type 1 diabetes mellitus and a singleton pregnancy were recruited from the obstetrical outpatient clinic of the University Medical Centre Utrecht, The Netherlands. The study subjects were asked to use the CGMS three times during pregnancy; between 10 and 12 weeks of gestation, between 24 and 28 weeks of gestation and between 34 and 36 weeks of gestation. Subjects were asked to perform four finger stick blood glucose measurements per day, which were used for calibration of the CGMS. They were advised to measure blood glucose levels before each meal and at bedtime. Twenty-nine women succeeded in using the CGMS three times during pregnancy. Data from these women were used for the present study. The 22 patients who did not complete three CGMS measurements either had an early spontaneous abortion (n=2), were recruited too late in pregnancy (n=5), delivered before the third measurement (n=5), or did not complete the study because of inconvenience (n=10).

Records were kept of complications during the pregnancy, gestational age at delivery, mode of delivery (vaginal delivery or caesarean section), birth weight and gender of the infant, presence of congenital malformations and neonatal hypoglycaemia (glucose <2.0 mmol/l). Large-for-gestational age (LGA) and extremely LGA were defined as a birth weight ≥ 90th and 97.7th centile, respectively, after correction for gender, parity and gestational age according to the Dutch growth charts (20). Fetal growth was measured fortnightly using ultrasound. Retrospectively, the ultrasound reports of the infants that LGA at birth were evaluated and a distinction was made between infants who were already LGA early in pregnancy (fetal growth parameters ≥95th centile ≤30 weeks of gestation) and late in pregnancy (fetal growth parameters <95th centile <30 weeks of gestation). The definition of early and late LGA used in this study was based on an ultrasound study in which it was found that fetal growth acceleration in LGA fetuses of diabetic mothers starts in the second trimester with a progressive increase >30 weeks of gestation when compared to normal size fetuses (21).

**Analysis**

Maternal and neonatal descriptives were compared between women with normal weight infants, women with a late LGA infant and women with an early LGA infant using Kruskal-Wallis or Chi-square statistics. If a p-value indicating a significant difference between any of the three study groups was found, additional post-hoc analysis was performed for differences between specific groups.

For each trimester of the pregnancy the median glucose levels for each hour of the day of each of the three subgroups were calculated. For each trimester of the pregnancy the 24-point diurnal glucose profiles of the three study groups were compared using repeated measurement analysis. This analysis was repeated on the data of the day of the CGMS measurement that second-best met the manufacturers accuracy criteria in those women with at least 48 hours of CGMS measurement.

Median glucose values and the coefficient of variance, a parameter for the description of the within-day variability (CV=100*SD/mean) were calculated for each 24-hour diurnal glucose profile and compared between the three study groups using Kruskal-Wallis statistics.

The relationship between the HbA1c-levels in the first, second and third trimester of the pregnancy and infant birth weight and the relationship between mean CGMS glucose level in the first, second and third trimester
of the pregnancy and infant birth weight was established using Spearman correlation. Infant birth weight was expressed as percentage of the population mean corrected for gender and gestational age. All analyses were performed using SPSS 12.0.1. (SPSS Inc, Chicago, Illinois, USA). For statistical evaluation, p-values <0.05 were considered significant.

RESULTS

Population characteristics and pregnancy outcome of the total study population of 29 women and of the three subgroups (normal birth weight, early LGA and late LGA) are given in Table 1. P-values indicate a difference between any of the three groups. Fifteen patients (52%) were pregnant for the first time. One patient developed pre-eclampsia. One patient experienced a hypoglycaemic coma in the first trimester of pregnancy. Sixty-four percent of the patients were delivered by caesarean section and 24% delivered before 37 weeks of gestation. One severely LGA infant died a few hours after birth due to asphyxia during labour. Fourteen infants (48%) were LGA at birth (weight ≥90th centile). Seven of these 14 infants were already LGA on ultrasound before 30 weeks of gestation. All of the early LGA infants had a birth weight ≥97.7th centile (extreme LGA). Only one of the 7 infants that became LGA after 30 weeks of gestation had a birth weight >97.7th centile. There was no significant difference in maternal age, pre-pregnancy BMI, duration of diabetes, age-of-onset of the diabetes, method of insulin administration, type of insulin and white classification between the normal weight, the late LGA and the early LGA infants (Table 1). Figure 1 shows the diurnal glucose profiles of the women who gave birth to a normal weight infant, a late LGA infant or an early LGA infant in the first, second and third trimester of pregnancy. Figure 1a represents all 29 women who participated in the study. Figure 1b shows the diurnal glucose profiles of the day of CGMS measurement that second-best met the manufacturers accuracy criteria of the women with at least 48 hours of measurement qualified for analysis. In both analyses (Figure 1a and 1b) repeated measurement analysis showed that there was a significant difference between the diurnal glucose profiles of the three study groups in the second trimester of pregnancy (p<0.05). Post hoc analysis showed that the diurnal glucose levels of the women with diabetes who gave birth to an early LGA infant were significantly higher than those of the women with diabetes who gave birth to a normal weight or a late LGA infant (p<0.05). In the first and third trimester there was no significant difference between the diurnal glucose profiles of any of the three study groups.

Table 2 shows that the median 24-hour glucose level was significantly higher in women who gave birth to an early LGA infant in all three trimesters of the pregnancy. Post hoc analysis of the median 24-hour glucose levels within the group of early LGA infants showed that the second trimester median glucose level was significantly higher than that in the first and third trimester (p<0.05). There was no significant difference in median 24-hour glucose levels between the three trimesters of pregnancy within the subgroups of women with a normal weight or a late LGA infant. There was no significant difference in within-day glucose variability between the three groups in either of the three trimesters of the pregnancy. No significant relation was found between mean 24-hour CGMS glucose level and infant birth weight percentage in either of the three trimesters of the pregnancy (rho=0.201, rho=0.241 and rho=0.145, respectively). Figure 2 shows that the relationship between HbA1c-levels and infant birth weight percentage was only significant in the third trimester of pregnancy. The median HbA1c-level was significantly higher in women who gave birth to an early LGA infant than in women who gave birth to a normal weight infant or a late LGA infant in all three trimesters of
the pregnancy but did not exceed 7.0% (Table 1).

DISCUSSION

This study shows a high percentage of LGA infants (48%) in women with type 1 diabetes, despite HbA1c-values within limits that are internationally considered to be safe (≤7.0%) in most of the cases (7). The infants who were extremely LGA at birth were already large-for-dates before 30 weeks of gestation. Moreover, in the second trimester of pregnancy, the mothers of these infants had significantly higher glucose levels during most of the day than the mothers of normal weight or late LGA infants. These findings indicate that growth in infants who become extreme LGA starts relatively early in pregnancy and is likely to be caused by elevated maternal glucose levels. Fetal macrosomia is associated with short term complications such as increased rates of caesarean section, shoulder dystocia and neonatal hypoglycaemia (10-12, 22-24). Long term complications for the infant include increased risks for obesity, diabetes and breast carcinoma later in life (25, 26).

In 1967, Pedersen introduced the concept of maternal hyperglycemia which reportedly increases the fetal secretion of insulin which in turn may cause LGA infants (27). Such an aetiology – although seemingly logical – appeared difficult to prove. It has been shown that elevated amniotic fluid insulin levels are associated with morbidity of the infant but a relation between maternal glucose levels and amniotic fluid insulin levels has yet to be established (28, 29). Maternal HbA1c-levels, which are an expression of mean glucose levels over the past 6-8 weeks, are not or poorly related to infant birth weight (centiles) and generally explain less than 10% of the variance in birth weight (9, 30, 31). In this study HbA1c-levels during the first and second trimester of pregnancy were not significantly related to infant birth weight. Third trimester HbA1c-levels were significantly but weakly related to infant birth weight (rho 0.571) and therefore can not entirely explain the variance in infant birth weight. Fasting glucose levels, in combination with maternal weight have been shown to explain only 12% of variance in birth weight while mean post-prandial blood glucose levels throughout pregnancy have been shown to explain about 40% of the variance in birth weight (30, 32). This suggests that post-prandial glycaemia rather than basal or mean glycaemia influences fetal growth and size at birth.

Recently it has been shown that HbA1c-levels do not correlate well with 24-hour glucose profiles as measured with the CGMS (33). This may explain the poor correlation between HbA1c-levels and infant birth weight. Moreover, it has also been shown that post-prandial glucose peaks may not be detected by routine glucose testing (34). So, the currently used measurement techniques appear to be inadequate for the assessment of maternal glucose profiles during pregnancy. This might explain the difficulties in establishing a reliable correlation between glucose control and infant birth weight. The CGMS overcomes these problems and in pregnant women with type 1 diabetes it has been shown that glucose levels measured with this device closely resemble maternal plasma glucose values (35). In a previous study with the CGMS we found that there are considerable day-to-day fluctuations in about half of the patients (19). In the present study we were able to study 24-hour glucose profiles in most women for at least two days in each trimester of pregnancy. The results of the analyses on the two days of CGMS measurement in each trimester were comparable, which strengthens our findings. We have also shown in previous study that self monitoring of blood glucose levels should be performed at least ten times a day to obtain glucose profiles that resemble that of the CGMS and to adequately obtain information of all daily glucose fluctuations (17). The performance of ten SMBG a day is costly and a burden for the patients. The CGMS can therefore be used as a tool to
regularly obtain additional information to that gathered with the daily SMBG measurements. The CGMS, however, was considered inconvenient by our patients, especially during the third trimester of pregnancy and in combination with continuous subcutaneous insulin infusion. Pregnant women with type 1 diabetes generally are very motivated to try to achieve (near) normoglycemia. This holds especially the periconceptional period and the first trimester of pregnancy, since glucose control is related to the incidence of congenital malformations. As a price to pay, the incidence of severe hypoglycaemic episodes increases, with a hypoglycaemic coma in up to 29% of the women (36, 37). It may well be that glucose control is somewhat loosened after the first trimester, just when insulin resistance is increasing. This study shows that the resulting higher glucose levels may induce early excessive growth, which is already evident on ultrasound examination before 30 weeks of gestation. Further investigation is needed to see whether early tight glycaemic control will reduce the number of extremely LGA infants.

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REFERENCES


### TABLES

**Table 1.** Maternal and neonatal descriptives of normal weight, late large-for-gestational age (LGA) and early LGA infants of women with type 1 diabetes mellitus

<table>
<thead>
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<th>Birth weight</th>
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<td></td>
<td>normal</td>
<td>late LGA</td>
<td>early LGA</td>
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<td>Number</td>
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<td>9</td>
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<td>Maternal descriptives</td>
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<tr>
<td>Maternal age (year)</td>
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<td>35.8 ± 3.6</td>
<td>34.9 ± 4.2</td>
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<td>Prepregnancy BMI (kg/m²)</td>
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<td>24.0 ± 3.9</td>
<td>26.7 ± 7.8</td>
<td>25.4 ± 3.8</td>
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<td>Insulin administration: mit/csii† (n)</td>
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<td>5 / 4</td>
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<td>Duration of diabetes (year)</td>
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<td>16.3 ± 9.2</td>
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<td>5 / 4</td>
<td>4 / 5</td>
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<td>3 / 4 / 1 / 1</td>
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<td>HbA₁c-level</td>
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<td>4 / 5</td>
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<td>Gestational age at birth (weeks)</td>
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<td>38.9 ± 1.6</td>
<td>37.2 ± 1.1</td>
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<td>Birth weight†† (g)</td>
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<td>2946 ± 454</td>
<td>3994 ± 181</td>
<td>4239 ± 173</td>
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<td>Birth weight centile††</td>
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<td>42 ± 22</td>
<td>95 ± 3</td>
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<td>Hypoglycaemia: yes/no (n)</td>
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<td>6 / 3</td>
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</table>

* Significant difference between any of the groups with p<0.05
† mit: multiple injection therapy; csii: continuous subcutaneous insulin infusion
†† Different by definition and therefore not included in the analysis
Table 2. Median glucose level of diurnal CGMS glucose profiles in women with a normal weight infant or with an early or late large-for-gestational age (LGA) infant, in the three trimesters of pregnancy.

<table>
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<th>Birth weight</th>
<th>Median CGMS glucose level (mmol/l)</th>
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<tr>
<td>normal</td>
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<tr>
<td></td>
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<td>6.2</td>
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<tr>
<td></td>
<td>trimester 3</td>
<td>5.6</td>
</tr>
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</table>

* Significant with p<0.05
FIGURE LEGENDS

Figure 1. (A) Median diurnal glucose profiles (midnight to midnight) in each trimester of pregnancy of women with diabetes after categorization based on infant birth weight using the day of the CGMS measurement that best met the manufacturers accuracy criteria (n=29). (B) Median diurnal glucose profiles (midnight to midnight) in each trimester of pregnancy of women with diabetes after categorization based on infant birth weight using the day of the CGMS measurement that second-best met the manufacturers accuracy criteria of the patients with more than one day of measurement suitable for analysis (trimester 1 n=26, trimester 2 n=23, trimester 3 n=20).
Figure 2. Relation between HbA\textsubscript{1c}-level and birth weight expressed as percentage of population mean corrected for gender and gestational age.