# Increased Second Trimester Maternal Glucose Levels Are Related to Extremely Large-for-Gestational-Age Infants in Women With Type 1 Diabetes

ANNELOES KERSSEN, MD, PHD[1]
HAROLD W. DE VALK, MD, PHD[2]
GERARD H.A. VISSER, MD, PHD[1]

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

**RESEARCH DESIGN AND METHODS** — Twenty-nine pregnant women with type 1 diabetes used the CGMS during each trimester of pregnancy. The glucose profiles of the women with a normal-weight infant or an LGA infant were compared.

**RESULTS** — Of the women with type 1 diabetes, 48% gave birth to an LGA infant. Fifty percent of these infants were already large for dates on ultrasound at <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-h glucose level was significantly higher in women who gave birth to early LGA infants in all three trimesters of pregnancy (6.7, 8.3, and 6.5 mmol/l for the first, second, and third trimesters, 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 is likely caused by increased maternal glucose levels. Further investigation is needed to see whether early tight glycemic control will reduce the number of extreme LGA infants.

*Diabetes Care* 30:1069–1074, 2007

Treatment of pregnant women with type 1 diabetes is aimed at achieving a pregnancy outcome that approximates that of nondiabetic 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 A1C levels within the limits advised by international guidelines (2,7).

The birth of large-for-gestational-age (LGA) infants (birth weight ≥90th centile) is 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 LGA infant rate is positively related to glycemic control (13–16). Discrepancy, however, exists concerning the trimester of pregnancy in which tight glucose regulation is considered the most important. Page et al. (14) conclude that the incidence of macrosomia may be reduced by tighter control of diabetes at conception and during the first trimester, 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 glycemic 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 glycemic control is the continuous glucose monitoring system (CGMS) (MiniMed, Sylmar, CA). This device measures glucose levels in the subcutaneous interstitial tissue fluid and makes continuous ambulatory monitoring of glucose profiles throughout pregnancy possible.

Given the uncertainty as to the relation of maternal glucose levels with infant birth weight, we used the CGMS to evaluate the glucose levels of pregnant women with type 1 diabetes in all three trimesters of pregnancy. We aimed at establishing the relationship between the diurnal glucose profiles, A1C levels, and birth weight of the infants born to these women.

## RESEARCH DESIGN AND METHODS

### CGMS

CGMS is a device that measures glucose levels through electro-chemical detection in the extracellular fluid of the abdominal subcutaneous tissue and stores values in a range of 2.2–22.2 mmol/l every 5 min for a maximum of 72 h. Besides interstitial glucose levels, the CGMS stores event

From the [1]Department of Perinatology and Gynaecology, University Medical Centre Utrecht, Utrecht, the Netherlands; and the [2]Department of Internal Medicine, University Medical Centre Utrecht, Utrecht, the Netherlands

Address correspondence and reprint requests to Anneloes Kerssen, Perinatology and Gynaecology, University Medical Centre Utrecht, KE.04.123.1, P.O. Box 85090, 3508 AB Utrecht, Netherlands. E-mail: anneloeskerssen@hotmail.com.

Received for publication 17 October 2005 and accepted in revised form 5 February 2007.

Published ahead of print at http://care.diabetesjournals.org on 23 February 2007. DOI: 10.2337/dc05-1985.

**Abbreviations:** CGMS, Continuous Glucose Monitoring System; LGA, large-for-gestational-age.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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 the following three criteria for optimal accuracy are met: *1*) at least four paired sensor glucose/meter glucose readings per 24 h, *2*) correlation coefficient between sensor glucose values and these four meter blood glucose readings ≥0.79, and *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 h were missing. The first 24 h 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 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 h 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, 51 pregnant women with type 1 diabetes 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 sex of the infant, and presence of congenital malformations and neonatal hypoglycemia (glucose <2.0 mmol/l).

LGA and extremely LGA infants were defined as a birth weight ≥90th and ≥97.7th centiles, respectively, after correction for sex, 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 were LGA at birth were evaluated and a distinction was made between infants who were already LGA early in pregnancy (fetal growth parameters ≥95th centile at ≤30 weeks of gestation) and late in pregnancy (fetal growth parameters <95th centile at <30 weeks of gestation). The definition of early and late LGA infants used in this study was based on an ultrasound study in which it was found that fetal growth acceleration in LGA fetuses of type 1 diabetic mothers starts in the second trimester, with a progressive increase at >30 weeks of gestation compared with normal-size fetuses (21).

## Analysis

Maternal and neonatal descriptions 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 $\chi^2$ 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-h 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 manufacturer's accuracy criteria in the women with ≥48 h of CGMS measurement.

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

The relationship between the A1C levels in the first, second, and third trimesters of pregnancy and infant birth weight and the relationship between mean CGMS glucose levels in the first, second, and third trimesters of pregnancy and infant birth weight were established using Spearman's rank correlation. Infant birth weight was expressed as percentage of the population mean corrected for sex and gestational age.

All analyses were performed using SPSS (version 12.0.1; SPSS, Chicago, IL). For statistical evaluation, *P* values <0.05 were considered significant.

**RESULTS** — Population characteristics and pregnancy outcomes of the total study population of 29 women and of the three subgroups of infants (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 type 1 diabetic patients (52%) were pregnant for the first time. One patient developed preeclampsia. One patient experienced a hypoglycemic 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 labor. Fourteen infants (48%) were LGA at birth (weight ≥90th centile). Of these 14 infants, 7 were already LGA on ultrasound before 30 weeks of gestation. All of the early LGA infants had a birth weight ≥97.7th centile (extremely LGA). Only one of the seven infants that became LGA after 30 weeks of gestation had a birth weight >97.7th centile. There was no significant difference in maternal age, prepregnancy BMI, duration of diabetes, age of onset of diabetes, method of insulin administration, type of insulin, and white classification between the normal-weight, late LGA, and early LGA infants (Table 1).

Figure 1 shows the diurnal glucose profiles of the women who gave birth to a normal-weight, late LGA, or early LGA infant in the first, second, and third trimesters of pregnancy. Figure 1*A* represents all 29 women who participated in the study; Fig. 1*B* shows the diurnal glucose pro-

**Table 1—*Maternal and neonatal descriptions of normal-weight, late LGA, and early LGA infants of women with type 1 diabetes***

| | Birth weight | | | |
|---|---|---|---|---|
| | Normal | Late LGA | Early LGA | *P** |
| *n* | 11 | 9 | 9 | — |
| Maternal descriptions | — | — | — | — |
| Maternal age (years) | 35.8 ± 3.6 | 34.9 ± 4.2 | 34.1 ± 4.6 | 0.669 |
| Prepregnancy BMI (kg/m$^2$) | 24.0 ± 3.9 | 26.7 ± 7.8 | 25.4 ± 3.8 | 0.695 |
| Insulin administration (MIT/CSII) | 6/5 | 5/4 | 5/4 | 0.992 |
| Duration of diabetes (years) | 9.6 ± 9.5 | 16.3 ± 9.2 | 19.1 ± 8.5 | 0.126 |
| Age of onset of diabetes (years) | 26.1 ± 11.1 | 18.6 ± 10.0 | 15.0 ± 7.4 | 0.136 |
| Type of insulin: human/analog | 9/2 | 5/4 | 4/5 | 0.221 |
| White classification: B/C/D/F | 7/1/2/1 | 3/4/1/1 | 1/5/2/1 | 0.101 |
| A1C level (%) | — | — | — | — |
| Trimester 1 | 6.2 ± 0.5 | 6.1 ± 0.4 | 7.0 ± 0.9 | 0.019 |
| Trimester 2 | 6.2 ± 0.5 | 6.1 ± 0.4 | 6.7 ± 0.5 | 0.045 |
| Trimester 3 | 6.1 ± 0.5 | 6.2 ± 0.5 | 7.0 ± 0.7 | 0.012 |
| Neonatal descriptions | — | — | — | — |
| Male/female | 5/6 | 5/4 | 4/5 | 0.845 |
| Gestational age at birth | 38.2 ± 1.2 | 38.9 ± 1.6 | 37.2 ± 1.1 | 0.090 |
| Birth weight† | 2,946 ± 454 | 3,994 ± 181 | 4,239 ± 173 | — |
| Birth weight centile† | 42 ± 22 | 95 ± 3 | 98 ± 0.1 | — |
| Hypoglycemia (yes/no) | 5/6 | 6/3 | 5/3 | 0.672 |

Data are means ± SD or *n* unless otherwise indicated. *Significant difference between any of the groups with $P < 0.05$. †Different by definition and therefore not included in the analysis. CSII, continuous subcutaneous insulin infusion; MIT, multiple injection therapy.

files—of the day of CGMS measurement that second best met the manufacturer's accuracy criteria—of the women with at least 48 h of measurement qualified for analysis. In both analyses (Fig. 1*A* and 1*B*), 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 type 1 diabetes who gave birth to an early LGA infant were significantly higher than those of the women with type 1 diabetes who gave birth to a normal-weight or late LGA infant ($P < 0.05$). In the first and third trimesters, there was no significant difference between the diurnal glucose profiles of any of the three study groups.

Table 2 shows that the median 24-h 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-h glucose levels within the group of early LGA infants showed that the second trimester median glucose level was significantly higher than those in the first and third trimesters ($P < 0.05$). There was no significant difference in median 24-h glucose levels between the three trimesters of pregnancy within the subgroups of women with a normal-weight or 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-h CGMS glucose level and infant–birth weight percentage in any of the three trimesters of the pregnancy ($\rho = 0.201$, $\rho = 0.241$, and $\rho = 0.145$, for the first, second, and third trimesters, respectively). Figure 2 shows that the relationship between A1C levels and infant birth weight percentage was only significant in the third trimester of pregnancy. The median A1C level was significantly higher in women who gave birth to an early LGA infant than in women who gave birth to a normal-weight or late LGA infant in all three trimesters of the pregnancy but did not exceed 7.0% (Table 1).

**CONCLUSIONS** — This study shows a high percentage of LGA infants (48%) in women with type 1 diabetes, despite A1C values within limits that are internationally considered to be safe (≤7.0%) in most 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 extremely 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 hypoglycemia (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 (27) introduced the concept of maternal hyperglycemia that reportedly increases the fetal secretion of insulin, which, in turn, may cause LGA infants. Such an etiology, 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 A1C levels, which are an expression of mean glucose levels over the past 6–8 weeks, are not or are poorly related to infant birth weight (centiles) and generally explain <10% of the variance in birth weight (9,30,31). In this study, A1C levels during the first and second trimesters of pregnancy were not significantly related to infant birth weight. Third trimester A1C levels were significantly but weakly related to infant birth

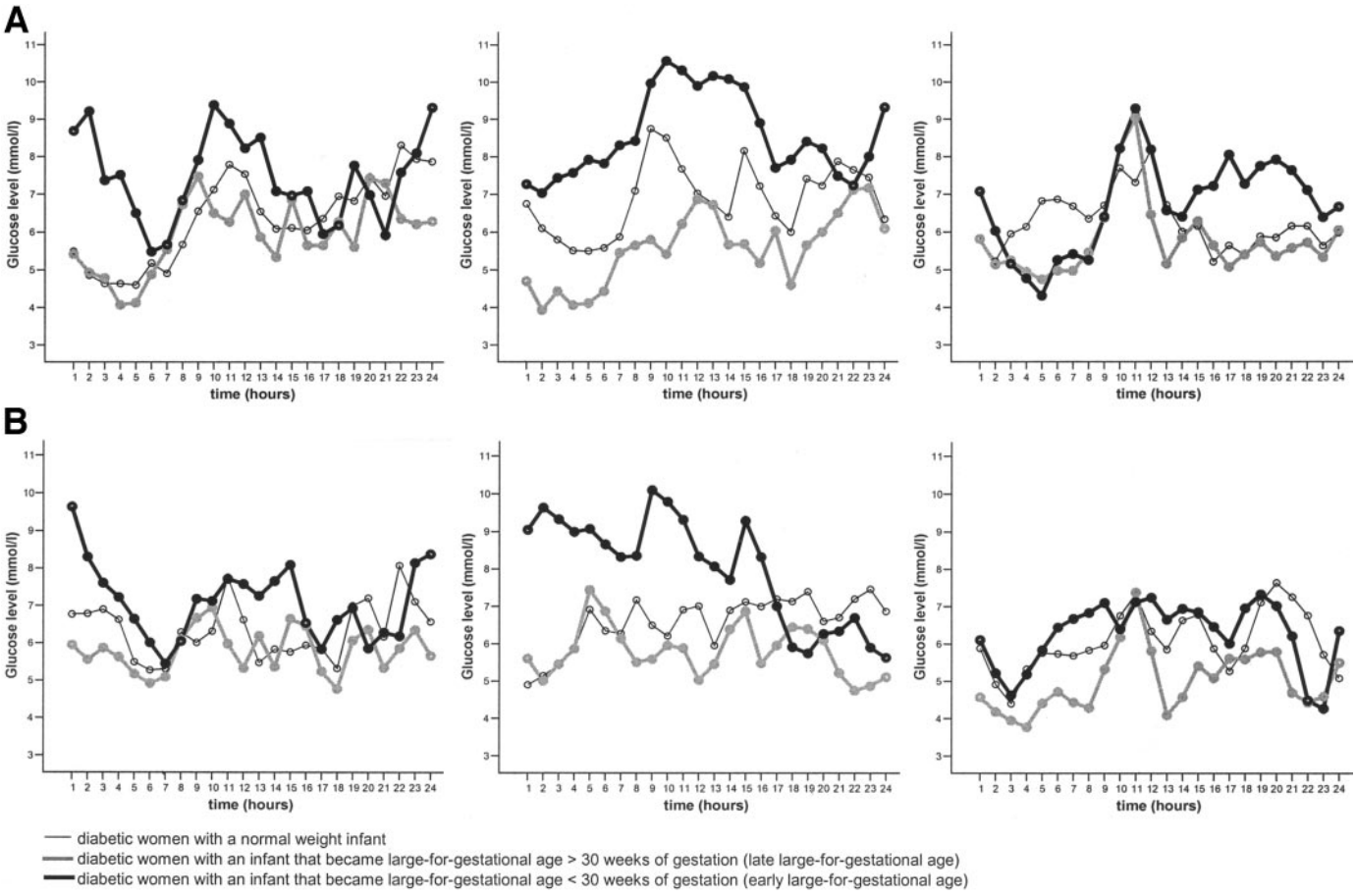


**Figure 1**—*Median diurnal glucose profiles (midnight to midnight) in each trimester of pregnancy of women with type 1 diabetes after categorization based on infant birth weight using the day of the CGMS measurement that best met the manufacturer's accuracy criteria* (n = *29)* (A) *and that second best met the manufacturer's accuracy criteria* (B) *of the patients with >1 day of measurement suitable for analysis (first trimester [*left panel*]* n = *26; second trimester [*center panel*]* n = *23; and third trimester [*right panel*]* n = *20).*

weight ($\rho = 0.571$) and therefore cannot 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 postprandial blood glucose levels throughout pregnancy have been shown to explain about 40% of the variance in birth weight (30,32). This suggests that postprandial glycemia rather than basal or mean glycemia influences fetal growth and size at birth.

Recently, it has been shown that A1C levels do not correlate well with 24-h glucose profiles as measured with the CGMS (33). This may explain the poor correlation between A1C levels and infant birth weight. Moreover, it has also been shown that postprandial glucose peaks may not be detected by routine glucose testing (34). Thus, 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 one-half of the patients (19). In the present study, we were able to study 24-h glucose profiles in most women for at least 2 days in each trimester of pregnancy. The results of the analyses on the 2 days of CGMS measurement in each trimester were comparable, which strengthens our findings. We have also shown, in a previous study, that self-monitoring of blood glucose levels should be performed at least 10 times a day to obtain glucose profiles that resemble those of the CGMS and to adequately obtain information of all daily glucose fluctuations (17). The performance of 10 self-monitorings of blood glucose a day is costly and a burden

**Table 2 —*Median glucose level of diurnal CGMS glucose profiles in women with a normal-weight infant or with an early or late LGA infant in the three trimesters of pregnancy***

| Median CGMS glucose level (mmol/l) | Birth weight | | | *P** |
|---|---|---|---|---|
| | Normal | Late LGA | Early LGA | |
| Trimester 1 | 5.7 | 6.0 | 6.7 | 0.014 |
| Trimester 2 | 6.2 | 5.7 | 8.3 | 0.000 |
| Trimester 3 | 5.6 | 5.8 | 6.5 | 0.027 |

*Significant with $P < 0.05$.

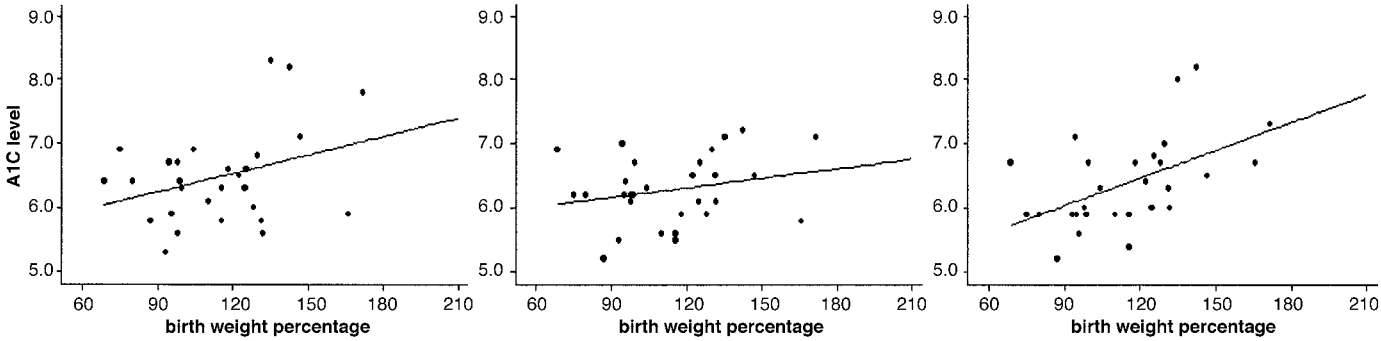


**Figure 2—***Relation between A1C level and birth weight expressed as the percentage of population mean corrected for sex and gestational age (first trimester [*left panel*] $\rho = 0.220$, P = not significant; second trimester [*center panel*] $\rho = 0.249$, P = not significant; and third trimester [*right panel*] $\rho = 0.519$, P $< 0.01$).*

for the patients. The CGMS can therefore be used as a tool to regularly obtain additional information to that gathered with the daily self-monitoring of blood glucose 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 for 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 hypoglycemic episodes increases, with a hypoglycemic 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 glycemic control will reduce the number of extremely LGA infants.

**Acknowledgments**— This study was supported by Novo Nordisk Farma, Alphen aan de Rijn, the Netherlands.

**References**

1. Diabetes care and research in Europe: the Saint Vincent Declaration. *Diabet Med* 7:360, 1990
2. Evers IM, de Valk HW, Visser GH: Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. *BMJ* 328: 915, 2004
3. Casson IF, Clarke CA, Howard CV, McKendrick O, Pennycook S, Pharoah PO, Platt MJ, Stanisstreet M, van Velszen D, Walkinshaw S: Outcomes of pregnancy in insulin dependent diabetic women: results of a five year population cohort study. *BMJ* 315:275–278, 1997
4. Hawthorne G, Robson S, Ryall EA, Sen D, Roberts SH, Ward Platt MP: Prospective population based survey of outcome of pregnancy in diabetic women: results of the Northern Diabetic Pregnancy Audit, 1994. *BMJ* 315:279–281, 1997
5. Penney GC, Mair G, Pearson DW: Outcomes of pregnancies in women with type 1 diabetes in Scotland: a national population-based study. *BJOG* 110:315–318, 2003
6. Platt MJ, Stanisstreet M, Casson IF, Howard CV, Walkinshaw S, Pennycook S, McKendrick O: St Vincent's Declaration 10 years on: outcomes of diabetic pregnancies. *Diabet Med* 19:216–220, 2002
7. American Diabetes Association: Preconception care of women with diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1):S76–S78, 2004
8. Berk MA, Mimouni F, Miodovnik M, Hertzberg V, Valuck J: Macrosomia in infants of insulin-dependent diabetic mothers. *Pediatrics* 83:1029–1034, 1989
9. Evers IM, de Valk HW, Mol BW, ter Braak EW, Visser GHA: Macrosomia despite good glycaemic control in type I diabetic pregnancy; results of a nationwide study in The Netherlands. *Diabetologia* 45: 1484–1489, 2002
10. Jolly MC, Sebire NJ, Harris JP, Regan L, Robinson S: Risk factors for macrosomia and its clinical consequences: a study of 350,311 pregnancies. *Eur J Obstet Gynecol Reprod Biol* 111:9–14, 2003
11. Boulet SL, Alexander GR, Salihu HM, Pass M: Macrosomic births in the United States: determinants, outcomes, and proposed grades of risk. *Am J Obstet Gynecol* 188:1372–1378, 2003
12. Meshari AA, De Silva S, Rahman I: Fetal macrosomia–maternal risks and fetal outcome. *Int J Gynaecol Obstet* 32:215–222, 1990
13. Landon MB, Gabbe SG, Piana R, Mennuti MT, Main EK: Neonatal morbidity in pregnancy complicated by diabetes mellitus: predictive value of maternal glycemic profiles. *Am J Obstet Gynecol* 156:1089–1095, 1987
14. Page RC, Kirk BA, Fay T, Wilcox M, Hosking DJ, Jeffcoate WJ: Is macrosomia associated with poor glycaemic control in diabetic pregnancy? *Diabet Med* 13:170–174, 1996
15. Mello G, Parretti E, Mecacci F, Pratesi M, Lucchetti R, Scarselli G: Excursion of daily glucose profiles in pregnant women with IDDM: relationship with perinatal outcome. *J Perinat Med* 25:488–497, 1997
16. Mello G, Parretti E, Mecacci F, La Torre P, Cioni R, Cianciulli D, Scarselli G: What degree of maternal metabolic control in women with type 1 diabetes is associated with normal body size and proportions in full-term infants? *Diabetes Care* 23:1494–1498, 2000
17. Kerssen A, de Valk HW, Visser GH: Do HbA1c levels and the self-monitoring of blood glucose levels adequately reflect glycaemic control during pregnancy in women with type 1 diabetes mellitus? *Diabetologia* 49:25–28, 2006
18. Mastrototaro J: The MiniMed Continuous Glucose Monitoring System (CGMS). *J Pediatr Endocrinol Metab* 12 (Suppl. 3): 751–758, 1999
19. Kerssen A, de Valk HW, Visser GH: Day-to-day glucose variability during pregnancy in women with type 1 diabetes mellitus: glucose profiles measured with the Continuous Glucose Monitoring System. *BJOG* 111:919–924, 2004
20. Kloosterman GJ: On intra-uterine growth. *Int J Gynecol Obstet* 8:895–912, 1970
21. Wong SF, Chan FY, Oats JJ, McIntyre DH: Fetal growth spurt and pregestational diabetic pregnancy. *Diabetes Care* 25:1681–1684, 2002
22. Cousins L: Pregnancy complications among

diabetic women: review 1965–1985. *Obstet Gynecol Surv* 42:140–149, 1987
23. Langer O, Berkus MD, Huff RW, Samueloff A: Shoulder dystocia: should the fetus weighing greater than or equal to 4000 grams be delivered by cesarean section? *Am J Obstet Gynecol* 165:831–837, 1991
24. Schaefer-Graf UM, Rossi R, Buhrer C, Siebert G, Kjos SL, Dudenhausen JW, Vetter K: Rate and risk factors of hypoglycemia in large-for-gestational-age newborn infants of nondiabetic mothers. *Am J Obstet Gynecol* 187:913–917, 2002
25. Van Assche FA, Holemans K, Aerts L: Fetal growth and consequences for later life. *J Perinat Med* 26:337–346, 1998
26. Samaras TT, Elrick H, Storms LH: Birthweight, rapid growth, cancer, and longevity: a review. *J Natl Med Assoc* 95:1170–1183, 2003
27. Pedersen J: Pathogenesis of the characteristic features of newborn infants of diabetic women. In *The Pregnant Diabetic and Her Newborn.* Baltimore, MD, Williams and Wilkins, 1967, p. 128–137
28. Weiss PA, Lichtenegger W, Winter R, Purstner P: Insulin levels in amniotic fluid: management of pregnancy in diabetes. *Obstet Gynecol* 51:393–398, 1978
29. Kainer F, Weiss PA, Huttner U, Haas J, Reles M: Levels of amniotic fluid insulin and profiles of maternal blood glucose in pregnant women with diabetes type-I. *Early Hum Dev* 49:97–105, 1997
30. Persson B, Hanson U: Fetal size at birth in relation to quality of blood glucose control in pregnancies complicated by pregestational diabetes mellitus. *Br J Obstet Gynaecol* 103:427–433, 1996
31. Johnstone FD, Mao JH, Steel JM, Prescott RJ, Hume R: Factors affecting fetal weight distribution in women with type I diabetes. *BJOG* 107:1001–1006, 2000
32. Parfitt VJ, Clark JD, Turner GM, Hartog M: Maternal postprandial blood glucose levels influence infant birth weight in diabetic pregnancy. *Diabetes Res* 19:133–135, 1992
33. Kerssen A, Evers IM, de Valk HW, Visser GHA: Poor glucose control in women with type 1 diabetes mellitus and 'safe' hemoglobin A1C values in the first trimester of pregnancy. *J Matern Fetal Neonat Med* 13:309–313, 2003
34. Kyne-Grzebalski D, Wood L, Marshall SM, Taylor R: Episodic hyperglycaemia in pregnant women with well-controlled type 1 diabetes mellitus: a major potential factor underlying macrosomia. *Diabet Med* 16:702–706, 1999
35. Kerssen A, de Valk HW, Visser GH: The Continuous Glucose Monitoring System during pregnancy of women with type 1 diabetes mellitus: accuracy assessment. *Diabetes Technol Ther* 6:645–651, 2004
36. Rosenn BM, Miodovnik M, Holcberg G, Khoury JC, Siddiqi TA: Hypoglycemia: the price of intensive insulin therapy for pregnant women with insulin-dependent diabetes mellitus. *Obstet Gynecol* 85:417–422, 1995
37. Evers IM, ter Braak EW, de Valk HW, van Der Schoot B, Janssen N, Visser GH: Risk indicators predictive for severe hypoglycemia during the first trimester of type 1 diabetic pregnancy. *Diabetes Care* 25: 554–559, 2002