Glucose control in pregnant women with type 1 diabetes mellitus

Studies using a continuous glucose monitoring system

Anneloes Kerssen

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Glucose control in pregnant women with type 1 diabetes mellitus

Studies using a continuous glucose monitoring system

Glucosehuishouding bij zwangere vrouwen met type 1 diabetes mellitus

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de Rector Magnificus, Prof. dr. W.H. Gispen, ingevolge het besluit van het College voor Promoties in het openbaar te verdedigen op

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Anneloes Kerssen

geboren op 5 november 1974 te Nuenen

Promotor: *Prof.dr. G.H.A. Visser*
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Department of Internal Medicine & Endocrinology
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Voorwoord

Wetenschap betekent de 'nauwkeurige en beredeneerde kennis van een bepaalde materie'. Dankzij de deelname van een groep zeer gemotiveerde vrouwen heb ik mijn kennis op het gebied van zwangerschap en type 1 diabetes mellitus kunnen verdiepen. Ik wil deze vrouwen hiervoor heel hartelijk bedanken. Ik hoop mijn opgedane kennis door te kunnen geven aan anderen door de uiteenzettingen in dit proefschrift. Daarnaast hoop ik dat de bevindingen uit dit proefschrift een bijdrage zullen leveren aan de behandeling van diabetes mellitus bij zwangere vrouwen. Dit zal hopelijk leiden tot een verbetering van de zwangerschapsuitkomst.

Anneloes Kerssen
Utrecht, april 2005

Aan mijn ouders
Voor Ruben en Jet

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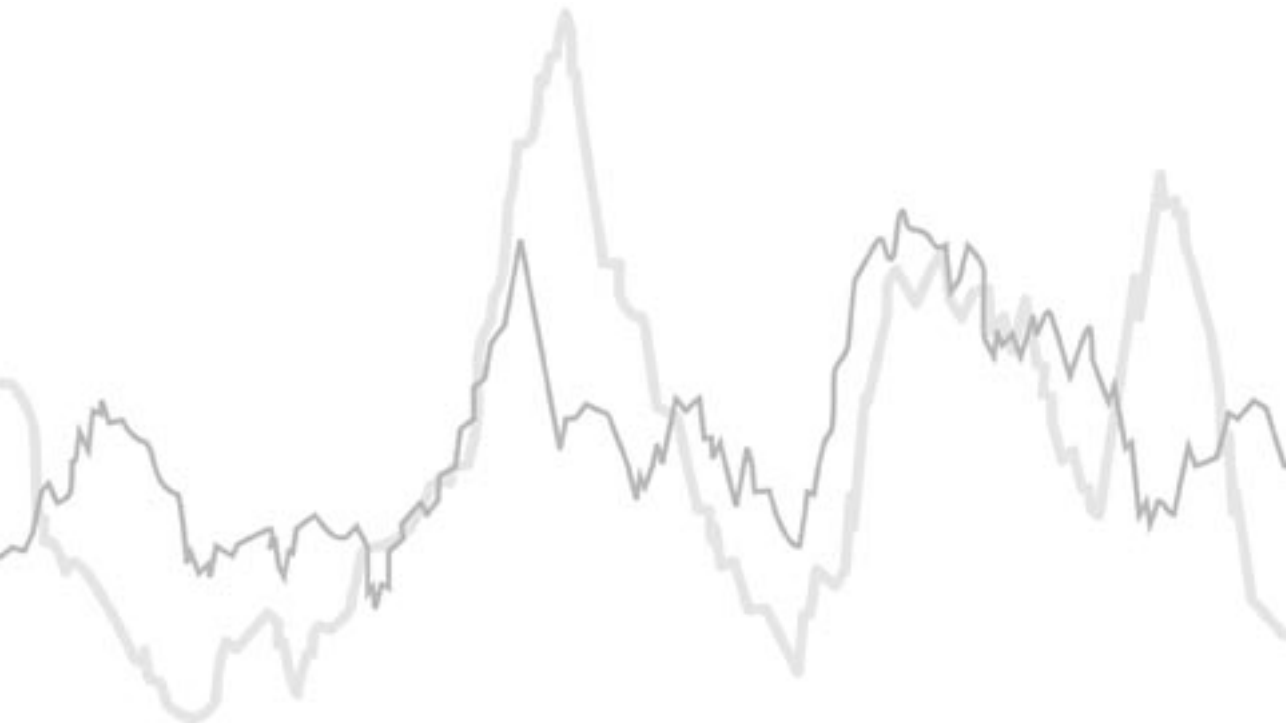
Introduction



Introduction

Pregnancy in women with type 1 diabetes mellitus has been associated with maternal, fetal and neonatal morbidity for a long time.[1] Treatment in these women should be aimed at achieving a pregnancy outcome that approximates that of healthy women.[2] It is commonly agreed that the morbidity decreases when diabetic control is tightened.[3-7] The most common methods for the determination of diabetic control are the self-monitoring of blood glucose levels (SMBG) and the measurement of HbA_{1c}-levels. SMBG is used for the observation of daily glucose levels while HbA_{1c}-levels give information on the glycaemic control of the patients over the previous two to three months.[8] The widely used guidelines of the American Diabetes Association (ADA) recommend a minimum of three SMBG per day during pregnancy.[9] The ADA guidelines also state that in women with diabetes, HbA_{1c}-levels within 1% above the normal range are acceptable during pregnancy.[10] These recommendations are based on several studies that have indicated that near-normal HbA_{1c}-levels are associated with rates of congenital malformations and spontaneous abortions that are no greater than rates found in the non-diabetic population.[11-15] Most of these studies, however, were conducted in selected populations often treated in specialised centres.[12-14]

In 1999-2000, a nation-wide study investigating pregnancy outcome in women with type 1 diabetes mellitus in the Netherlands, was conducted at our department.[16] In this prospective unselected cohort based study, a total of 323 pregnant women with type 1 diabetes from 118 hospitals participated. Eighty-four percent of the pregnancies were planned and folic-acid supplementation was adequate in 70%. HbA_{1c}-levels in early pregnancy were ≤7.0% in 75% of the study population. Maternal and neonatal complication rates, however, were considerably higher when compared to the rates in the general population (*Table 1* and *Table 2*).[16] The macrosomia rate (birth weight ≥90th centile) was four times that of the background population while the incidence of congenital malformations was triple that of the background population. The capacity of HbA_{1c}-levels to predict macrosomia appeared to be weak (explained variance <10%). The high complication rates were surprising taking into account the high percentages of women with 'safe' HbA_{1c}-levels, planned pregnancies en folic-acid intake.
Over the last decade, several other unselected, population-based studies on outcomes of pregnancies in women with type 1 diabetes have been published (*Table 3*).[17-20] In the diabetic population the relative risk of stillbirth and perinatal mortality was three to six times that of the background population. Infants of women with type 1 diabetes had a two to ten-fold greater risk of having a congenital malformation than infants of healthy women. In all studies the distribution of birthweight was shifted markedly to the right compared to the reference population. Unfortunately, in three of the four studies, no mention was made of the

degree of diabetic control during these pregnancies. Hawthorne *et al*. showed that, although 63% of the pregnancies were planned and pre-pregnancy advice was given in 80% of the planned pregnancies, only 29% of the women achieved good diabetic control. A major difficulty pointed out by Hawthorne *et al*. was the lack of a standardised measure of diabetic control before and during pregnancy.[17]

Table 1. Maternal outcome of pregnancies complicated by type 1 diabetes mellitus compared to national Dutch data

	Type 1 diabetes mellitus	National data
Pre-eclampsia (%)	12.7	1.05*†
Prematurity (%)	32.2	7.1*
Caesarean section (%)	44.3	12.0*
Maternal mortality (%)	0.6	0.01*‡

*p<0.05, †National data of 1995-1996, ‡ National data of 1996-1998

Table 2. Perinatal outcome of pregnancies complicated by type 1 diabetes mellitus compared to national Dutch data.

	Type 1 diabetes mellitus	National data
Congenital malformations (%)	8.8	2.6*
- major	5.5	-
- minor	3.3	-
Perinatal mortality (%)	2.8	0.8*
Macrosomia (%)	45.1	10.0*

* p<0.05

The most frequent complication of type 1 diabetes during pregnancy is macrosomia.[16,17,21] Macrosomia is associated with maternal complications such as higher rates of prolonged first and second stages of labour, an increased risk of instrumental vaginal delivery, shoulder dystocia, caesarean birth, third and fourth-degree perineal lacerations and postpartum hemorrhage.[22,23] Neonatal complications associated with macrosomia include fractures of the clavicula, Erbs palsy, hypoglycaemia, infant respiratory distress syndrome (IRDS) and hyperbilirubinaemia.[24-26] Macrosomia is likely to be caused by maternal (and fetal) hyperglycaemia, although correlations with maternal HbA_{1c}-levels are low.[27-31] However, macrosomia is associated with high levels of fetal insulin in the amniotic fluid and it may well be that post-prandial glucose peaks are not reflected by HbA_{1c} percentages.[32] It has also been shown that post-prandial glucose peaks may not be detected by routine glucose testing.[33] Other major perinatal complications seen in women with type 1

Table 3. Pregnancy outcome in unselected population based studies of pregant women with type 1 diabetes mellitus.

	design	n	stillbirth*	perinatal mortality*	congenital malformations*	birthweight	glycaemic control (HbA_{1c}-level)
Casson *et al.* 1997	population cohort	462	2.5/0.5	3.6/0.8	9.4/0.9	mean 1.38 SD >mean background population	-
Hawthorne *et al.* 1997	prospective population cohort	113	1.9/0.6	4.8/0.9	4.8/1.6	35% >p95	in reference range: 29% moderate control: 49% poor control: 22%
Platt *et al.* 2002	population cohort	547	3.0/0.5	4.3/0.8	8.4/0.8	mean 1.31 SD >mean background population	-
Penney *et al.* 2003	prospective population-based cohort	273	1.9/0.5	2.8/0.8	6.0/2.8	mean 1.57 SD >mean background population	-

* Data are % in diabetic population / % in backround population

diabetes include sudden intra-uterine death of the fetus, congenital malformations and neonatal hypoglycaemia.[17-20] All these complications seem to be associated with intermittent hyperglycaemia of the mother during pregnancy. Intra-uterine fetal death is most likely based on impaired ripening of the placenta, resulting in chronic fetal hypoxemia.[34] When, as a result of hyperglycaemia in the mother, glucose levels in the hypoxic fetus increase, anaerobic glycolysis will result in fetal lactate accumulation and eventually in fetal death. Clinical studies have indicated that the most important alteration in the embryonic environment capable of inducing congenital malformations is an increase in glucose concentration.[35-39] Glucose levels have a number of direct metabolic, possibly teratogenic, consequences for the embryo and the development of congenital malformations is, therefore, dependent on blood glucose levels during embryogenesis. Neonatal hypoglycaemia is most likely due to pancreatic islet cell hyperplasia caused by intermittent hyperglycaemia during pregnancy.[40] This results in hyperinsulinaemia which, besides acting as a growth factor, causes hypoglycaemia after birth when maternal glucose supply stops abruptly.

All the major complications seen in pregnancies of women with type 1 diabetes seem to be associated with intermittent hyperglycaemia. We hypothesised that these hyperglycaemic episodes are short and post-prandial and are not monitored on routine daily testing (SMBG). In pregnancies of women with type 1 diabetes, the incidence of hypoglycaemic episodes is also increased.[41-44] It is conceivable that the alternating hypo- and hyperglycaemic episodes are of little influence on HbA_{1c}-levels as these can be considered as a mean over a 120-day period.[8] This would explain the finding that complication rates remain high, despite achieving adequate diabetic control as currently defined in international guidelines. A close look at maternal glucose levels during pregnancy in women with type 1 diabetes is necessary to explore this hypothesis. Secondly, close observation of maternal glucose levels in non-diabetic women is necessary to define normoglycaemia during pregnancy.
A novel device for the monitoring of glucose levels in the home setting is the Continuous Glucose Monitoring System (CGMS). This device measures glucose levels in the subcutaneous interstitial tissue fluid every five minutes during three days and makes continuous ambulatory monitoring of glucose profiles throughout the pregnancy possible.

Aim of the thesis

Given the uncertainty as to the association between (abnormal) glucose levels and pregnancy outcome in women with type 1 diabetes mellitus, we started this PhD project.

The thesis was aimed at answering the following questions:

1) Can glucose levels of pregnant women with type 1 diabetes mellitus be measured reliably using the Continuous Glucose Monitoring System (CGMS)?
2) What are normal glucose levels throughout gestation when measured with the CGMS?
3) What is the relation between HbA_{1c}-levels, glucose profiles obtained with fingerstick measurement and diurnal glucose profiles measured with the CGMS in pregnant women with type 1 diabetes mellitus?
4) Can birth weight be predicted by the weight of an earlier born infant in women with type 1 diabetes mellitus?
5) What is the relationship between diurnal glucose profiles and occurrence of fetal macrosomia in pregnant women with type 1 diabetes mellitus?

Outline of the thesis

Performance of the CGMS

In *Chapter 2* the accuracy of the CGMS is evaluated by comparing glucose levels measured with the CGMS with capillary self-monitored blood glucose levels. In *Chapter 3* the reproducibility of the CGMS is evaluated by comparing glucose profiles of two CGMS devices worn simultaneously.

Healthy women

The results of a longitudinal study in which the diurnal glucose profiles were measured in healthy pregnant women are described in *Chapter 4*.

Women with type 1 diabetes mellitus

The relationship between within-day variability of glucose levels and HbA_{1c}-level in the first trimester of pregnancy is described in *Chapter 5*. In *Chapter 6* the accuracy of the HbA_{1c}-levels currently described as 'safe' during pregnancy and the number of self-monitored blood glucose values that have to be obtained daily to give an accurate idea of glucose levels, are studied. The degree of day-to-day variability in glucose profiles and the effect of this variability on treatment of the diabetes are described in *Chapter* 7. The usefulness of three-day instead of two-day continuous glucose measurements is described in *Chapter 8*. The value of older sibling birth weight and mean HbA_{1c}-level during pregnancy as predictors of macrosomia is described in *Chapter 9*. Diurnal glucose profiles during the three trimesters of pregnancy are related to infant birth weight in *Chapter 10*.

Chapter 11 contains a summary, conclusions and recommendations for the future.

References

1. Duncan JM. On Puerperal Diabetes. *Trans Obstet Soc Lond* 1882;24:256-285.
2. Diabetes care and research in Europe: the Saint Vincent declaration. *Diabet Med* 1990;7:360.
3. Goldman JA, Dicker D, Feldberg D, Yeshaya A, Samuel N, Karp M. Pregnancy outcome in patients with insulin-dependent diabetes mellitus with preconceptional diabetic control: a comparative study. *Am J Obstet Gynecol* 1986;155:293-297.
4. Kitzmiller JL, Gavin LA, Gin GD, Jovanovic-Peterson L, Main EK, Zigrang WD. Preconception care of diabetes. Glycemic control prevents congenital anomalies. *JAMA* 1991;265:731-736.
5. Kitzmiller JL, Buchanan TA, Kjos S, Combs CA, Ratner RE. Pre-conception care of diabetes, congenital malformations, and spontaneous abortions. *Diabetes Care* 1996;19:514-541.
6. Gold AE, Reilly R, Little J, Walker JD. The effect of glycemic control in the pre-conception period and early pregnancy on birth weight in women with IDDM. *Diabetes Care* 1998;21:535-538.
7. Dunne FP. Pregestational Diabetes Mellitus and Pregnancy. *Trends Endocrinol Metab* 1999;10:179-182.
8. Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Clin Chem* 2002;48:436-472.
9. Standards of Medical Care in Diabetes. *Diabetes Care* 2005;28:S4-S36.
10. ADA. Preconception care of women with diabetes. *Diabetes Care* 2004;27 Suppl 1:S76-S78.
11. Miller E, Hare JW, Cloherty JP, Dunn PJ, Gleason RE, Soeldner JS, Kitzmiller JL. Elevated maternal hemoglobin A_{1c} in early pregnancy and major congenital anomalies in infants of diabetic mothers. *N Engl J Med* 1981;304:1331-1334.
12. Ylinen K, Aula P, Stenman UH, Kesaniemi-Kuokkanen T, Teramo K. Risk of minor and major fetal malformations in diabetics with high haemoglobin A_{1c} values in early pregnancy. *Br Med J (Clin Res Ed)* 1984;289:345-346.
13. Key TC, Giuffrida R, Moore TR. Predictive value of early pregnancy glycohemoglobin in the insulin-treated diabetic patient. *Am J Obstet Gynecol* 1987;156:1096-1100.
14. Greene MF, Hare JW, Cloherty JP, Benacerraf BR, Soeldner JS. First-trimester hemoglobin A1 and risk for major malformation and spontaneous abortion in diabetic pregnancy. *Teratology* 1989;39:225-231.
15. Pregnancy outcomes in the Diabetes Control and Complications Trial. *Am J Obstet Gynecol* 1996;174:1343-1353.
16. Evers IM, de Valk HW, Visser GHA. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. *BMJ* 2004;328:915.
17. 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* 1997;315:279-281.
18. 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* 2002;19:216-220.
19. Penney GC, Mair G, Pearson DW. Outcomes of pregnancies in women with type 1 diabetes in Scotland: a national population-based study. *BJOG* 2003;110:315-318.
20. 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* 1997;315:275-278.

21. Berk MA, Mimouni F, Miodovnik M, Hertzberg V, Valuck J. Macrosomia in infants of insulin-dependent diabetic mothers. *Pediatrics* 1989;83:1029-1034.

22. 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* 2003;111:9-14.

23. Stotland NE, Caughey AB, Breed EM, Escobar GJ. Risk factors and obstetric complications associated with macrosomia. *Int J Gynaecol Obstet* 2004;87:220-226.

24. Mountain KR. The infant of the diabetic mother. *Baillieres Clin Obstet Gynaecol* 1991;5:413-442.

25. Weintrob N, Karp M, Hod M. Short- and long-range complications in offspring of diabetic mothers. *J Diabetes Complications* 1996;10:294-301.

26. Mulik V, Usha Kiran TS, Bethal J, Bhal PS. The outcome of macrosomic fetuses in a low risk primigravid population. *Int J Gynaecol Obstet* 2003;80:15-22.

27. 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* 1996;103:427-433.

28. Schwartz R, Gruppuso PA, Petzold K, Brambilla D, Hiilesmaa V, Teramo KA. Hyperinsulinemia and macrosomia in the fetus of the diabetic mother. *Diabetes Care* 1994;17:640-648.

29. Fraser R. Diabetic control in pregnancy and intrauterine growth of the fetus. *Br J Obstet Gynaecol* 1995;102:275-277.

30. Jovanovic-Peterson L, Peterson CM, Reed GF, Metzger BE, Mills JL, Knopp RH, Aarons JH. Maternal postprandial glucose levels and infant birth weight: the Diabetes in Early Pregnancy Study. The National Institute of Child Health and Human Development--Diabetes in Early Pregnancy Study. *Am J Obstet Gynecol* 1991;164:103-111.

31. Johnstone FD, Mao JH, Steel JM, Prescott RJ, Hume R. Factors affecting fetal weight distribution in women with type I diabetes. *BJOG* 2000;107:1001-1006.

32. Weiss PA, Lichtenegger W, Winter R, Purstner P. Insulin levels in amniotic fluid. Management of pregnancy in diabetes. *Obstet Gynecol* 1978;51:393-398.

33. 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* 1999;16:702-706.

34. Evers IM, Nikkels PG, Sikkema JM, Visser GHA. Placental pathology in women with type 1 diabetes and in a control group with normal and large-for-gestational-age infants. *Placenta* 2003;24:819-825.

35. Fuhrmann K, Reiher H, Semmler K, Glockner E. The effect of intensified conventional insulin therapy before and during pregnancy on the malformation rate in offspring of diabetic mothers. *Exp Clin Endocrinol* 1984;83:173-177.

36. Leslie RDG, Pyke DA, John PN, White JM. Hemoglobin A1 in diabetic pregnancy. *Lancet* 1978;ii:958-959.

37. Schaefer UM, Songster G, Xiang A, Berkowitz K, Buchanan TA, Kjos SL. Congenital malformations in offspring of women with hyperglycemia first detected during pregnancy. *Am J Obstet Gynecol* 1997;177:1165-1171.

38. Levine AB. Reproductive health in diabetic women. A report of two cases demonstrating the importance of preconception care. *J Reprod Med* 1998;43:691-692.

39. McElvy SS, Miodovnik M, Rosenn B, Khoury JC, Siddiqi T, Dignan PS, Tsang RC. A focused preconceptional and early pregnancy program in women with type 1 diabetes reduces perinatal mortality and malformation rates to general population levels. *J Matern Fetal Med* 2000;9:14-20.

40. Taylor R, Lee C, Kyne-Grzebalski D, Marshall SM, Davison JM. Clinical outcomes of pregnancy in women with type 1 diabetes(1). *Obstet Gynecol* 2002;99:537-541.

41. Kimmerle R, Heinemann L, Delecki A, Berger M. Severe hypoglycemia incidence and predisposing factors in 85 pregnancies of type I diabetic women. *Diabetes Care* 1992;15:1034-1037.

42. 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* 1995;85:417-422.

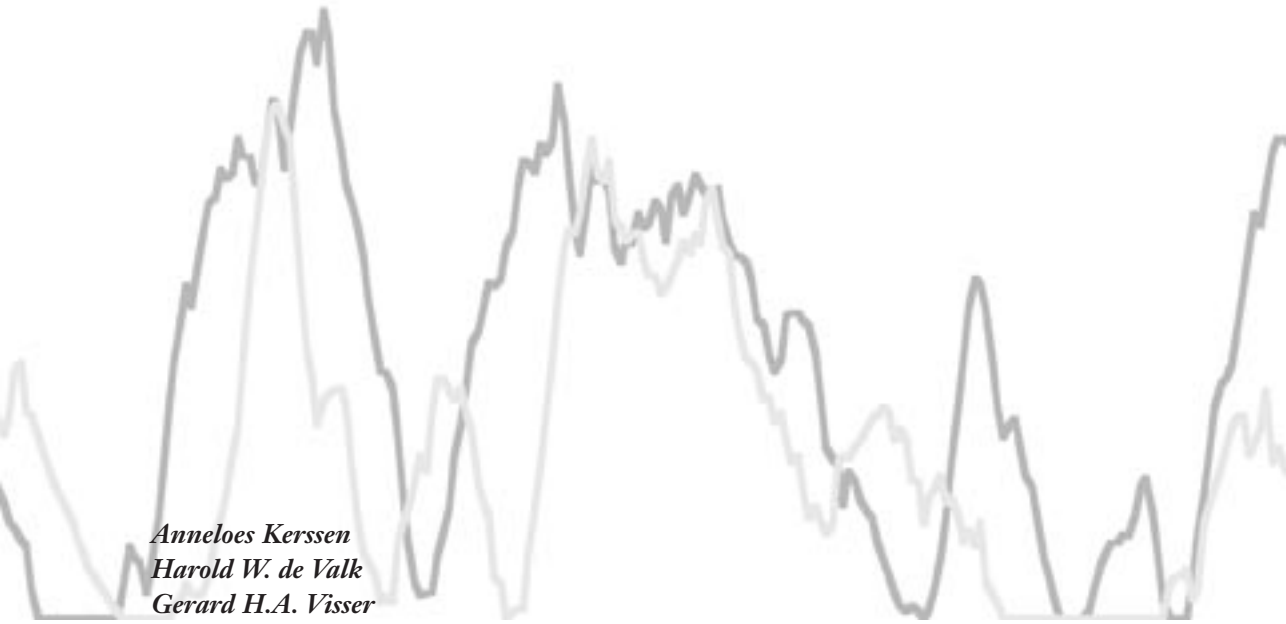
43. Hellmuth E, Damm P, Molsted-Pedersen L, Bendtson I. Prevalence of nocturnal hypoglycemia in first trimester of pregnancy in patients with insulin treated diabetes mellitus. *Acta Obstet Gynecol Scand* 2000;79:958-962.

44. Evers IM, ter Braak EW, de Valk HW, van Der Schoot B, Janssen N, Visser GHA. Risk indicators predictive for severe hypoglycemia during the first trimester of type 1 diabetic pregnancy. *Diabetes Care* 2002;25:554-559

2

The Continuous Glucose Monitoring System during pregnancy of women with type 1 diabetes mellitus;

accuracy assessment



Anneloes Kerssen
Harold W. de Valk
Gerard H.A. Visser

Abstract

Objective The Continuous Glucose Monitoring System (CGMS) allows close monitoring of glucose patterns and might be helpful in explaining the persistence of high complication rates in pregnancies of women with type 1 diabetes. It was the aim of this study to determine whether the CGMS accurately reflects glucose levels in pregnant women with type 1 diabetes mellitus.

Methods Fifteen pregnant women with type 1 diabetes used the CGMS and were asked to determine at least seven fingerstick blood glucose levels each day, of which four were used for calibration. The patients were asked to keep a diary of the non-calibration blood glucose values. The accuracy of the CGMS was studied by comparing the non-calibration blood glucose values to simultaneously measured sensor glucose values using the Pearson correlation coefficient, the mean of absolute differences and the Clarke error-grid analysis.

Results A total of 239 non-calibration blood glucose values were analysed. Correlation coefficient between non-calibration blood glucose and sensor glucose value was 0.94 ($p<0.001$). Mean of absolute difference was 0.74 mmol/l. Of the non-calibration data 93.8% fell in the clinically acceptable zone of the Clarke error-grid analysis.

Conclusion The CGMS is an accurate tool for additional glucose monitoring in pregnant women with type 1 diabetes mellitus.

Introduction

With the persistence of increased rates of macrosomia and congenital malformations in infants born to women with type 1 diabetes mellitus who are well regulated according to conventional standards (i.e. HbA_{1c}-level ≤1% above the upper limit of normal range), more frequent measurements of glucose levels are necessary.[1-3] Determination of glucose levels in subcutaneous tissue fluid is a less invasive alternative for blood glucose measurements. Continuous subcutaneous glucose monitoring allows identification of glucose excursions and can be combined with details of everyday activities. Patterns and trends observed with the continuous measurement might be helpful in explaining complications and in adjustment of treatment.

Currently, several methods for determination of glucose levels in subcutaneous tissue fluid are available: (1) electrochemical detection, (2) microdialysis, and (3) reverse iontophoresis.[4,5] As reverse iontophoresis does not seem to be accurate concerning the detection of hypoglycaemia and as microdialysis is not patient-friendly in use due to size of the device and diameter of the insertion needle, our focus is currently on electrochemical detection with use of the Continuous Glucose Monitoring System (CGMS, MiniMed, Sylmar, CA 91342, USA).[4,6]

Research has shown that interstitial fluid glucose levels are 20-50% lower than blood glucose levels.[7] Calibration of the CGMS with capillary glucose levels enables the system to correct for this difference.[8] However, clinical performance and reproducibility of the CGMS have been reported to be unsatisfactory in some non-pregnant diabetic populations.[9-11] It was the objective of this study to determine whether the CGMS accurately reflects glucose levels in pregnant women with type 1 diabetes mellitus.

Materials and methods

The Continuous Glucose Monitoring System

The CGMS has three components: a sterile disposable glucose sensor, a glucose monitor and a connecting cable. A communication station (Com-Station) is needed to download the data stored in the monitor to a personal computer. The sensor consists of a thin, one centimetre long flexible polyurethane tube that houses the glucose-sensing electrode. The sensor measures interstitial glucose as an electrical potential created by the reaction of glucose oxidase with glucose. The sensor signal is acquired every ten seconds and an average of the acquired signals is saved in the monitor every five minutes. The monitor stores values within a range of 2.2-22.2 mmol/l (40-400mg/dl) providing 288 readings in 24 hours. Maximum recording interval is suggested as 72 hours. Besides interstitial glucose levels, the monitor stores event markers for meals, insulin injections and exercise.

The electrical readings acquired by the sensor are converted into glucose levels (mmol/l) when downloaded from the monitor to a personal computer. To be able to determine a calibration factor, at least four fingerstick blood glucose levels need to be entered into the monitor each 24 hours.
The data of 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 day, 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%.[8]

Methods

Fifteen pregnant women with type 1 diabetes mellitus were asked to use the CGMS for three days. They were asked to determine at least seven fingerstick blood glucose levels each day of which four were used for calibration. Patients were asked not to enter the non-calibration blood glucose values in the monitor but to keep a diary of the values with the exact time of determination. After downloading the CGMS data, the non-calibration capillary glucose values were matched with synchronously measured CGMS glucose values. The accuracy of the CGMS was analysed using the Pearson correlation coefficient (*r*), the mean of absolute differences (MAD) and the Clarke error-grid analysis.[12] The error-grid analysis (EGA) describes the accuracy of glucose measurement systems over the entire range of glucose values taking into account the absolute value of the system-generated glucose value, the absolute value of the reference blood glucose value, the relative difference between the two values and the clinical significance of this difference. The EGA defines the x-axis as the reference (blood) glucose value and the y-axis as the determined (sensor) glucose value. The data obtained fall into different accuracy zones on the EGA (*Figure 1*). Zone A, sensor glucose values deviating from the reference blood glucose values less than 20% or both sensor and reference value ≤3.9 mmol/l. Zone B, sensor values deviating from reference values >20% but not leading to treatment adjustments. Zone C, sensor values resulting in over correction of acceptable glucose levels. Zone D, dangerous failure to detect and treat glucose levels. Zone E, wrongful treatment of glucose levels.[12] Glucose values in zone A and B are considered clinically acceptable whereas errors in zones C, D and E are considered potentially dangerous since they may lead to wrong treatment decisions.

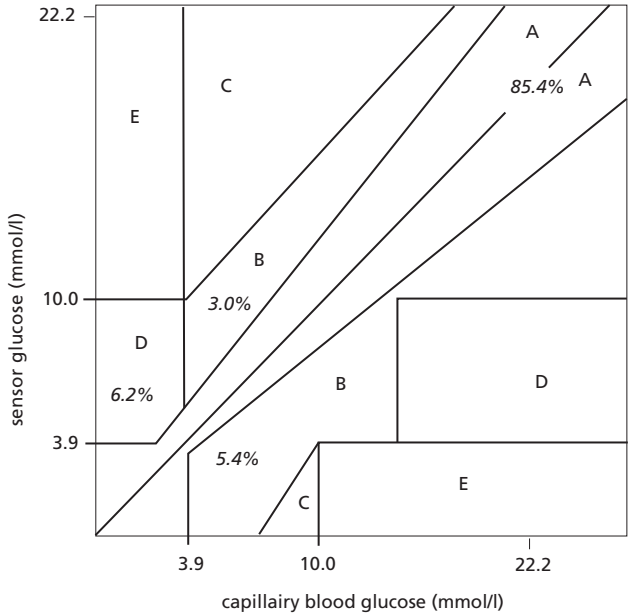


Figure 1. Zones of the Clarke error-grid with percentage of non-calibration pairs of data in each zone.

Results

All 15 pregnant women with type 1 diabetes mellitus who were asked for this study participated. There were no adverse events associated with the use of the CGMS. Mean age of the patients was 34.4 years (range 29.8 to 39.2 years) and mean HbA_{1c}-level was 6.4% (range 5.3 to 7.5%). Of the patients six, four and five were in their first, second and third trimester of pregnancy, respectively.

There were 45 sensor days in the 15 women who participated. In seven women one day did not meet the criteria for optimal accuracy; two days had an average value of differences between sensor glucose values and meter glucose values >28% and of 5 days data collection during the 24 hours was incomplete. Thus, there were 38 days available for analysis.

Each 24-hours, four calibration blood glucose values (total 152) and three to 12 additional non-calibration capillary blood glucose values (total 239) were available for analysis. Pearson correlation coefficient for relation between blood glucose and sensor glucose value was 0.94 ($p<0.001$) and 0.96 ($p<0.001$) for the non-calibration and calibration pairs of data, respectively (*Figure 2*).

MAD was 0.74 and 0.63 mmol/l for non-calibration and calibration pairs of data, respectively. The results of the error grid analysis for the non-calibration pairs of data are as follows: zone A 85.4%; zone B 8.4%; zone C 0%; zone D 6.2%; zone E 0% (*Figure 1*). *Figure 3* shows two graphical examples of 24-hours of sensor glucose values and all meter glucose values.
Post-hoc analysis of the 15 pairs of data classified in zone D with clinically non-acceptable errors (6.2%) shows that this error occurred in seven of the 15 patients. In all cases the blood glucose value was lower than the sensor glucose value. In 5 of these pairs of data the patients (n=4) experienced a hypoglycaemia (symptomatic and blood glucose level ≤3.9 mmol/l) within one hour after insulin injection while sensor glucose levels did not fall below the hypoglycaemia limit. In the 10 other pairs of data, the blood glucose level ranged from 2.6 to 3.6 mmol/l while sensor glucose values ranged from 4.1 to 4.9 mmol/l. In these cases patients (n=6) did not experience a hypoglycaemia, but had hypoglycaemic blood glucose levels at regular measurement time points.

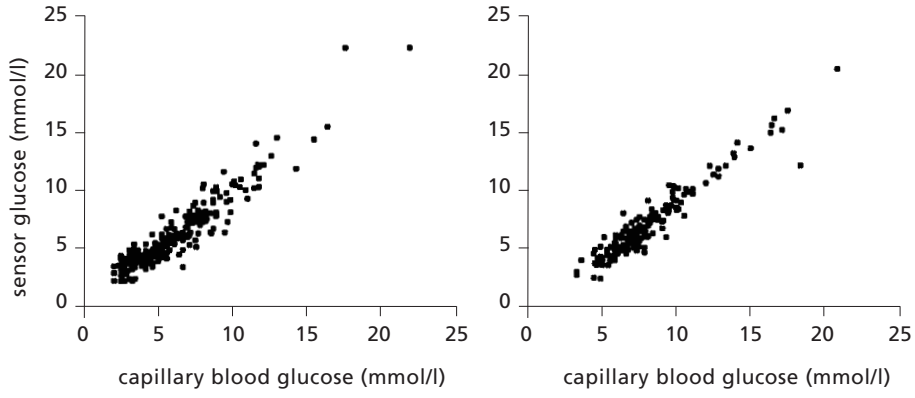


Figure 2. a) Relation between capillary blood glucose and sensor glucose values of non-calibration data (r=0.94, p<0.001). b) Relation between capillary blood glucose and sensor glucose values of calibration data (r=0.96, p<0.001).

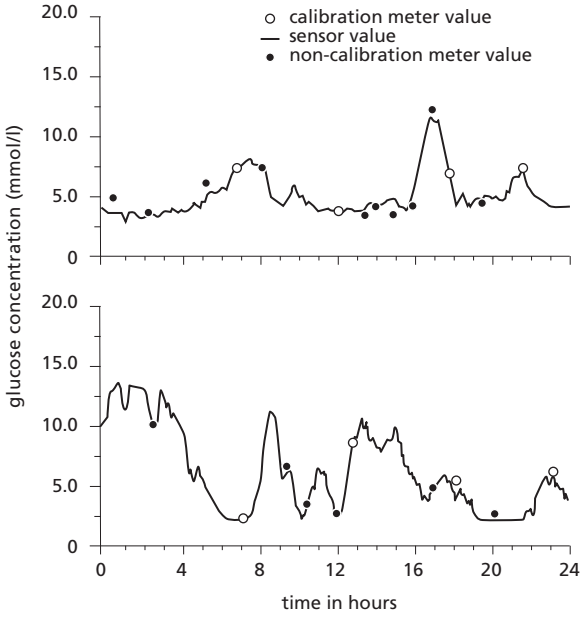


Figure 3. Twenty-four hour graphical profiles with sensor glucose values and all meter glucose values of two patients.

Discussion

Our results illustrate that in pregnant women with type 1 diabetes mellitus, continuous subcutaneous glucose measurements with the CGMS are accurate when compared to capillary fingerstick measurements since 93.8% of the data are in the clinically acceptable zone of the EGA.

Analysis of the pairs of data classified in zones with clinically not acceptable errors shows blood glucose values in the hypoglycaemic range (≤3.9 mmol/l) while sensor glucose values are in the normal range (3.9-7.8 mmol/l). Aussedat *et al.*[13] have shown in rat studies that during insulin induced hypoglycaemia the decrease in interstitial glucose was less marked than that of plasma glucose. This can be explained by a difference in glucose kinetics between blood and interstitial fluid. The blood glucose level is the result of endogenous (hepatic) glucose production and exogenous glucose administration minus the elimination of glucose by the kidney and output of glucose to the interstitial tissue. Interstitial glucose level is the result of input from the vascular compartment minus the output into the surrounding cells. In patients with diabetes the primary defence against hypoglycaemia is catecholamines.[14] Theoretically it is conceivable that in hyperinsulinaemic hypoglycaemia, catecholamines partially suppress the effect of insulin on glucose transport from interstitial tissue to cells, delaying and reducing the decrease in

interstitial glucose level.[13] Furthermore additional effects due to alterations in subcutaneous blood flow during hypoglycaemia cannot be ruled out, although an increase and a decrease during hypoglycaemia have both been described.[15-18] Finally, it may also be argued that, due to measurement errors, home-fingerstick capillary blood glucose levels are not always representative for plasma blood glucose levels.[19-21]

Several reports have cast doubt on the accuracy of home-monitoring devices in pregnant diabetics with glucose levels ranging up to 8.0 mmol/l.[22,23] It has been suggested that lower hematocrite levels combined with metabolic and physiological changes during pregnancy interfere with the accuracy of these home-monitoring devices.[22] Furthermore, two studies conducted in a non-pregnant diabetic population evaluating the accuracy of blood glucose meters when used in the hypoglycaemic range (≤3.9 mmol/l) show that there is a substantial difference between different blood glucose meters.[24,25] In the hypoglycaemic range none of the blood glucose meters used in these studies met the criteria recommended by the American Diabetes Association (target variability not exceeding 5% and total error of less than 15%).[24-26] Since fingerstick home-monitored blood glucose levels were used as standard in this study, this lack of accuracy might be problematic. However, in the normo- and hyperglycaemic range home-monitoring devices have tested to be accurate with a total error <15%.[27,28] The use of fingerstick glucose testing for this study, therefore, seems acceptable, at least for values above the hypoglycaemic range.

The presence of a time lag ranging from 15 to 55 minutes between blood glucose and interstitial fluid glucose levels during recovery from hypoglycaemia has been described as an obstacle in continuous subcutaneous glucose measurement.[7,13,29,30] The design of our study was insufficient to reveal this aspect. However, the findings in literature showing an overestimation of hypoglycaemia by the CGMS [7,13,29,30] and the findings showing an increased risk of developing hypoglycaemia during pregnancy in women with type 1 diabetes,[31,32] imply that the CGMS is only an additional tool and not a replacement of fingerstick capillary glucose measurements during pregnancy.

CGMS performance statistics are better in patients with type 1 diabetes than in patients with type 2 or gestational diabetes.[33] This can be accounted for by a difference in glucose variability between patients with different types of diabetes. The CGMS glucose concentrations are calculated in retrospect using a regression analysis of the blood glucose values with corresponding sensor readings for each calendar day.[8] The regression coefficient calculated in the calibration is strongly influenced by variations in the blood glucose values used to calculate them and becomes more accurate when the range of values rises. It has been demonstrated that pregnancy in women with type 1 diabetes is complicated by within-day glucose variability larger than outside pregnancy.[34] This may explain the very high level of accuracy of the CGMS seen in this study.

In conclusion, the CGMS is an accurate tool for *additional* glucose measurements in pregnant women with type 1 diabetes, at least in situations in which the MiniMed accuracy criteria are met. Treatment decisions should, however, not be based on CGMS measurements alone as this can lead to clinically unacceptable treatment errors as the CGMS occasionally misleads in the hypoglycaemic range.

References

1. 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* 2002;45:1484-1489.
2. ADA. Preconception care of women with diabetes. *Diabetes Care* 2003;26 Suppl 1:S91-S93.
3. Suhonen L, Hiilesmaa V, Teramo K. Glycaemic control during early pregnancy and fetal malformations in women with type I diabetes mellitus. *Diabetologia* 2000;43:79-82.
4. Kerner W. Implantable glucose sensors: present status and future developments. *Exp Clin Endocrinol Diabetes* 2001;109 Suppl 2:S341-346.
5. Robert JJ. Continuous monitoring of blood glucose. *Horm Res* 2002;57 Suppl 1:81-84.
6. Pitzer KR, Desai S, Dunn T, Edelman S, Jayalakshmi Y, Kennedy J, Tamada JA, Potts RO. Detection of hypoglycemia with the GlucoWatch biographer. *Diabetes Care* 2001;24:881-885.
7. Rebrin K, Steil GM, van Antwerp WP, Mastrototaro JJ. Subcutaneous glucose predicts plasma glucose independent of insulin: implications for continuous monitoring. *Am J Physiol* 1999;277:E561-571.
8. Mastrototaro J. The MiniMed Continuous Glucose Monitoring System (CGMS). *J Pediatr Endocrinol Metab* 1999;12 Suppl 3:751-758.
9. Metzger M, Leibowitz G, Wainstein J, Glaser B, Raz I. Reproducibility of glucose measurements using the glucose sensor. *Diabetes Care* 2002;25:1185-1191.
10. Guerci B, Floriot M, Bohme P, Durain D, Benichou M, Jellimann S, Drouin P. Clinical Performance of CGMS in Type 1 Diabetic Patients Treated by Continuous Subcutaneous Insulin Infusion Using Insulin Analogs. *Diabetes Care* 2003;26:582-589.
11. The accuracy of the CGMS in children with type 1 diabetes: results of the diabetes research in children network (DirecNet) accuracy study. *Diabetes Technol Ther* 2003;5:781-789.
12. Clarke WL, Cox D, Gonder-Frederick LA, Carter W, Pohl SL. Evaluating clinical accuracy of systems for self-monitoring of blood glucose. *Diabetes Care* 1987;10:622-628.
13. Aussedat B, Dupire-Angel M, Gifford R, Klein JC, Wilson GS, Reach G. Interstitial glucose concentration and glycemia: implications for continuous subcutaneous glucose monitoring. *Am J Physiol Endocrinol Metab* 2000;278:E716-728.
14. Evans ML, Amiel SA. *Hypoglycaemia* (ed. Amiel, SA) (Oxford University Press, Oxford, 2002).
15. Aman J, Berne C, Ewald U, Tuvemo T. Cutaneous blood flow during a hypoglycaemic clamp in insulin-dependent diabetic patients and healthy subjects. *Clin Sci (Lond)* 1992;82:615-618.
16. Fernqvist-Forbes E, Linde B, Gunnarsson R. Insulin absorption and subcutaneous blood flow in normal subjects during insulin-induced hypoglycemia. *J Clin Endocrinol Metab* 1988;67:619-623.
17. Hilsted J, Bonde-Petersen F, Madsbad S, Parving HH, Christensen NJ, Adelhoj B, Bigler D, Sjontoft E. Changes in plasma volume, in transcapillary escape rate of albumin and in subcutaneous blood flow during hypoglycaemia in man. *Clin Sci (Lond)* 1985;69:273-277.

18. Hilsted J, Madsbad S, Sestoft L. Subcutaneous blood flow during insulin-induced hypoglycaemia: studies in juvenile diabetics with and without autonomic neuropathy and in normal subjects. *Clin Physiol* 1982;2:323-332.

19. Henry MJ, Major CA, Reinsch S. Accuracy of self-monitoring of blood glucose: impact on diabetes management decisions during pregnancy. *Diabetes Educ* 2001;27:521-529.

20. Raine CH, 3rd. Self-monitored blood glucose: a common pitfall. *Endocr Pract* 2003;9:137-139.

21. Colagiuri R, Colagiuri S, Jones S, Moses RG. The quality of self-monitoring of blood glucose. *Diabet Med* 1990;7:800-804.

22. Harkness LJ, Ashwood ER, Parsons S, Lenke RR. Comparison of the accuracy of glucose reflectance meters in pregnant insulin-dependent diabetics. *Obstet Gynecol* 1991;77:181-185.

23. Moses R, Schier G, Matthews J, Davis W. The accuracy of home glucose meters for the glucose range anticipated in pregnancy. *Aust N Z J Obstet Gynaecol* 1997;37:282-286.

24. Zenobi PD, Keller A, Jaeggi-Groisman SE, Glatz Y. Accuracy of devices for self-monitoring of blood glucose including hypoglycemic blood glucose levels. *Diabetes Care* 1995;18:587-588.

25. Trajanoski Z, Brunner GA, Gfrerer RJ, Wach P, Pieber TR. Accuracy of home blood glucose meters during hypoglycemia. *Diabetes Care* 1996;19:1412-1415.

26. ADA. Self-monitoring of blood glucose. *Diabetes Care* 1994;17:81-86.

27. Blood glucose monitors. *Health Devices* 1988;17:253-271.

28. Tate PF, Clements CA, Walters JE. Accuracy of home blood glucose monitors. *Diabetes Care* 1992;15:536-538.

29. Monsod TP, Flanagan DE, Rife F, Saenz R, Caprio S, Sherwin RS, Tamborlane WV. Do sensor glucose levels accurately predict plasma glucose concentrations during hypoglycemia and hyperinsulinemia? *Diabetes Care* 2002;25:889-893.

30. Cheyne EH, Cavan DA, Kerr D. Performance of a continuous glucose monitoring system during controlled hypoglycaemia in healthy volunteers. *Diabetes Technol Ther* 2002;4:607-613.

31. Evers IM, ter Braak EW, de Valk HW, van der Schoot B, Janssen N, Visser GHA. Risk indicators predictive for severe hypoglycemia during the first trimester of type 1 diabetic pregnancy. *Diabetes Care* 2002;25:554-559.

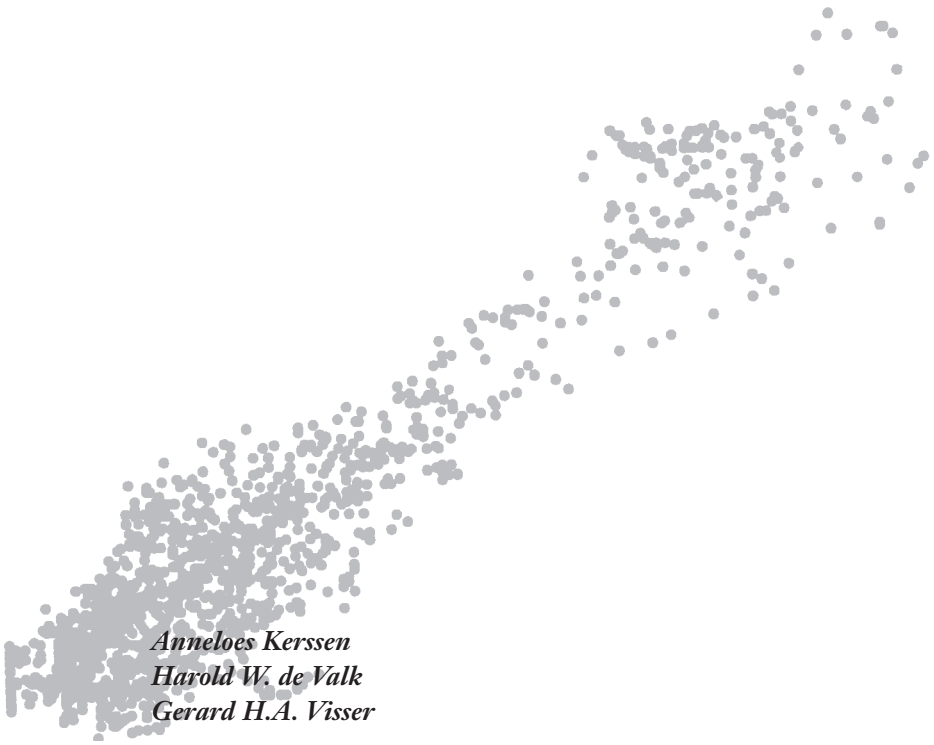
32. Hellmuth E, Damm P, Molsted-Pedersen L, Bendtson I. Prevalence of nocturnal hypoglycemia in first trimester of pregnancy in patients with insulin treated diabetes mellitus. *Acta Obstet Gynecol Scand* 2000;79:958-962.

33. Gross TM, Ter Veer A. Continuous glucose monitoring in previously unstudied population subgroups. *Diabetes Technol Ther* 2000;2 Suppl 1:S27-34.

34. Kerssen A, Evers IM, Valk de HW, Visser GHA. Poor glucose control in women with type 1 diabetes mellitus and 'safe' hemoglobin A_{1c} values in the first trimester of pregnancy. *J Matern Fetal Neonat Med* 2003;13:309-313.

3

Validation of the Continuous Glucose Monitoring System by the use of two CGMS simultaneously in pregnant women with type 1 diabetes mellitus



Anneloes Kerssen
Harold W. de Valk
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Abstract

Objective In pregnant women with type 1 diabetes tight glycaemic control reduces perinatal complications. Intensive observation of glucose profiles is essential in the achievement of tight glycaemic control. The recent availability of the Continuous Glucose Monitoring System (CGMS) creates the opportunity to obtain more complete glucose profiles. This study was aimed at evaluating the accuracy of the CGMS in pregnant women with type 1 diabetes.

Methods Five pregnant women with type 1 diabetes were asked to use two CGMS simultaneously. The simultaneously measured glucose levels were analysed using Pearson correlation, the mean absolute difference and Bland-Altman analysis. Secondly the percentage of concordance of paired data in the hypoglycaemic, normoglycaemic or hyperglycaemic range was calculated.

Results The correlation coefficient between simultaneously measured data was 0.94 ($P<0.001$). The mean absolute difference was 1.1±0.8 mmol/l. Bland-Altman analysis shows that 95% of the data pairs have a difference ≤1.74 mmol/l. Almost 80% of the data pairs could be classified in the same glucose range. In 81% of the non-concordant pairs, one glucose value was classified in the hypoglycaemic range and one in the normoglycaemic range.

Conclusion This study shows that the reproducibility of the CGMS in pregnant women with type 1 diabetes is adequate. This indicates that the CGMS is a useful tool in the management of type 1 diabetes in pregnant women. However, the CGMS should only be used as a supplementary method of daily glucose level measurement as a small degree of error, mainly in the hypoglycaemic range, is present.

Introduction

Intensive diabetes management is necessary in pregnant women with type 1 diabetes mellitus since tight glycaemic control has been shown to reduce maternal and neonatal complications.[1-3] Regular self-monitoring of blood glucose levels (SMBG) combined with personalized insulin regimens are used to optimise glycaemic control. SMBG, however, has its limitations since the intermittent measurements give an incomplete picture of blood glucose fluctuations over the day. The availability of continuous glucose monitoring systems gives the opportunity to obtain more complete glucose profiles. The Continuous Glucose Monitoring System (CGMS) was one of the first systems available for clinical use.

In non-pregnant diabetic subjects the accuracy of the CGMS has been tested.[4-11] The correlation coefficient between sensor glucose and meter blood glucose levels has been reported to range from 0.76 to 0.81.[5,8] Error grid analyses have shown that 95-99% of the glucose levels measured with the CGMS do not lead to differences in treatment strategies when compared to blood glucose levels.[7,9]

Comparison of two CGMS devices used simultaneously, this far, has been restricted to non-pregnant diabetic patients, with a correlation coefficient of 0.84.[4,7] The CGMS has a higher detection rate of hyperglycaemic and hypoglycaemic episodes compared to intermittent fingerstick blood glucose measurement.[9] However, the usefulness of the CGMS as hypoglycaemia detector is still on debate as the accuracy of the device seems to decrease when glucose levels are in the hypoglycaemic range.[5,6,10]

In a previous report we have shown that the performance of the CGMS in pregnant women with type 1 diabetes is accurate since the correlation coefficient with meter blood glucose values was 0.94 ($p<0.001$) and since 94% of the measurements did not lead to differences in treatment strategies when compared to self-monitored blood glucose levels.[11] So far this has been the only study evaluating the accuracy of the CGMS in pregnant women with type 1 diabetes.

The aim of the present study was to further explore the accuracy of the CGMS in pregnant women with type 1 diabetes by comparing the glucose profiles of two CGMS devices worn simultaneously.

Materials and methods

The Continuous Glucose Monitoring System

The CGMS has three components: a sterile disposable glucose sensor, a glucose monitor and a connecting cable. A communication station (Com-Station) is needed to download the data stored in the monitor to a personal computer. The sensor consists of a thin, one centimetre long flexible polyurethane tube that houses the glucose-sensing electrode. The sensor measures interstitial glucose as an electrical

potential created by the reaction of glucose oxidase with glucose. The sensor signal is acquired every ten seconds and an average of the acquired signals is saved in the monitor every five minutes. The monitor stores values within a range of 2.2-22.2 mmol/l (40-400mg/dl) providing 288 readings in 24 hours. Maximum recording interval is suggested to be 72 hours. Besides interstitial glucose levels, the monitor stores event markers for meals, insulin injections and exercise.
The electrical readings acquired by the sensor are converted into glucose levels (mmol/l) when downloaded from the monitor to a personal computer. To be able to determine a calibration factor, at least four finger stick blood glucose values need to be entered into the monitor each 24 hours.
The data of 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 day, 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 $\leq 28\%$.[12] 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.

Methods

Five pregnant women with type 1 diabetes mellitus (gestational age 25-32 weeks) participated in this study. Each patient was asked to use two CGMS devices simultaneously for at least 24 hours. The CGMS devices were placed symmetrically on the left and right side of the abdomen. Three patients used continuous subcutaneous insulin infusion (CSII) and two used multiple injections as method of insulin therapy. In the patients using CSII, the CGMS was inserted at a distance of at least ten centimetres from the insertion site of the pump catheter. The patients were asked to determine a minimum of four SMBG per day that were used for the calibration of the CGMS.

Analysis

According to the American Diabetes Association (ADA) consensus statement, SMBG devices should have a total error (analytic and user) of preferably no more than 5% and at the most 15% at glucose concentrations between 1.7 and 22.2 mmol/l.[13] This specific performance goal is defined for the comparison of blood glucose values measured with SMBG devices with glucose values measured in a laboratory.[13] No consensus exists as to which degree of difference is acceptable when two SMBG devices or two CGMS devices are compared during simultaneous use. We therefore used several methods in the analyses:
1) Pearson correlation coefficients of the paired sensor glucose values.
2) The mean absolute difference between paired sensor glucose values.
3) Simultaneously measured CGMS glucose readings were compared using

Bland-Altman analysis.[14] With the latter analysis the difference of two simultaneous measurements on the same subject is plotted against the mean of the two measurements and the '95% limits of agreement' are calculated. These limits will include the difference between the two measurements on the same subject with a probability of 95%.

4) Concordance in the simultaneous measurements of each patient was determined by calculating the percentage of data that could both be classified in one of the following categories: A) hypoglycaemic range (glucose value ≤3.9 mmol/l); B) normoglycaemic range (glucose values 3.9-7.8 mmol/l); C) hyperglycaemic range (glucose value ≥7.8 mmol/l).[15,16]

Results

Use and performance of the CGMS according to the MiniMed criteria

The CGMS measurement period ranged from 26 to 76 hours. Two of the three patients using CSII removed the CGMS after completing only one 24-hour period as the use of three devices attached to the abdomen (two CGMS devices and one insulin pump) was too uncomfortable, especially during the night. As the study group was small and the influence of each patient on the results should be equal, we decided to use one 24-hour period of each patient. Of the patients with more than 24-hours of CGMS measurement we used the first complete 24-hour period (from midnight to midnight) that was available. Thus, 288 paired sensor-sensor data per patient (1440 in total) were analysed. The agreement between sensor glucose readings and meter glucose readings was, according to the MiniMed performance criteria, good. There were 23 paired sensor-meter glucose values. The correlation coefficients between sensor and meter glucose levels were 0.98, both for the CGMS used on the left and the one used on the right side of the abdomen. The mean value of differences between sensor glucose values and meter blood glucose values was 9.9% (range 1-26%) and 11.2% (range 0.6-27%) for the CGMS used on the left and right, respectively.

Reproducibility of the CGMS

The simultaneously measured CGMS glucose profiles of all five patients are shown in *Figure 1*. *Table 1* shows the correlation coefficients and significance levels of CGMS glucose levels measured per patient. The 1440 paired sensor values combined correlated significantly, r=0.94, p<0.001 (*Figure 2*). The mean absolute difference in glucose levels was 1.1±0.8 mmol/l (*Table 2*). Comparison of the data using Bland-Altman analysis indicated a 95% probability limit range of ±1.74 mmol/ (range -1.96 to 1.52 mmol/l, *Figure 3*). When the glucose values measured with the CGMS were classified as being in the hypoglycaemic, normoglycaemic or hyperglycaemic range, 79% of the data pairs were concordant (*Table 3*). In 81% of the pairs of data that were not concordant, one glucose value was classified as in the hypoglycaemic range and the other was classified as in the normoglycaemic range (*Table 3*).

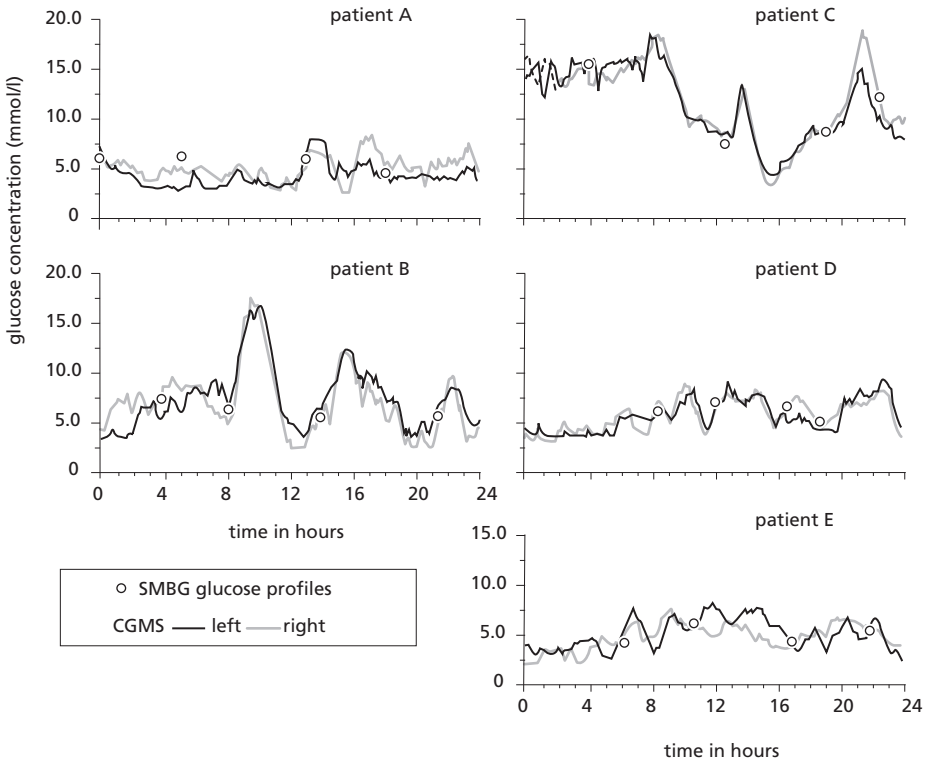

Figure 1. Glucose profiles of pregnant women with type 1 diabetes using two CGMS simultaneously

Table 1. Correlation coefficients and significance levels of CGMS glucose values measured on the left and the right side of the abdomen simultaneously.

Patient	Pearson correlation coefficient	Significance
A	0.58	0.000*
B	0.87	0.000*
C	0.94	0.000*
D	0.84	0.000*
E	0.56	0.000*
Total	0.94	0.000*

* significant with $p < 0.001$

Table 2. Mean absolute difference of simultaneously measured CGMS glucose values.

Patient	Mean absolute difference*
A	1.1 ± 0.7
B	1.4 ± 0.9
C	1.0 ± 0.9
D	0.7 ± 0.5
E	1.1 ± 0.8
Total	1.1 ± 0.8

* mean and SD in mmol/l

Table 3. Concordance of simultaneously measured glucose values after classification into hypoglycaemic, normoglycaemic and hyperglycaemic range.

Patient	concordant *	of the non-concordant values		
		1 normoglycaemic and 1 hypoglycaemic*	1 normoglycaemic and 1 hyperglycaemic*	1 hypoglycaemic and 1 hyperglycaemic*
A	77.8	84	16	0
B	70.8	71	23	7
C	96.2	73	27	0
D	75.3	70	30	0
E	72.9	95	5	0
Total	78.6	81	17	2

* percentage (%)

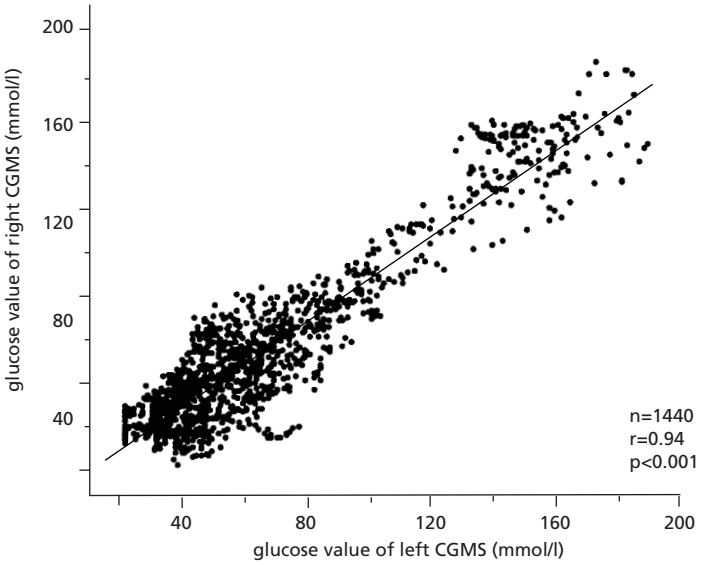

Figure 2. Correlation of CGMS glucose values measured on the left and right side of the abdomen simultaneously.

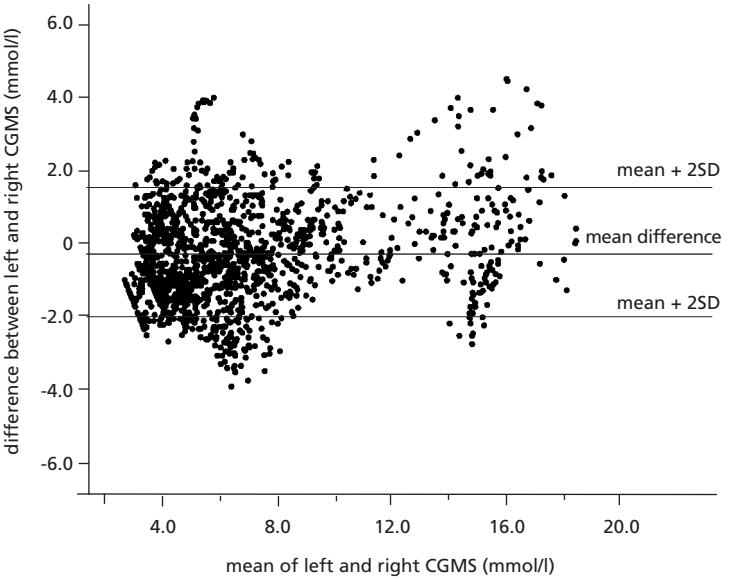

Figure 3. Bland-Altman plot of the data showing the difference between the two simultaneous measured CGMS glucose values on the y-axis and the mean of the two simultaneously measured CGMS glucose values on the x-axis.

Discussion

Data on simultaneous use of two CGMS devices this far have been restricted to two studies including only fifteen non-pregnant patients with type 1 diabetes.[4,7] The use of two devices is a burden to the patients and volunteers are difficult to get. Our data are the first observing the reproducibility of the CGMS during pregnancy in patients with type 1 diabetes mellitus.

The simultaneous use of two CGMS devices should, ideally, give two identical glucose profiles. The results of the present study show that the profiles are indeed strongly related (Pearson correlation coefficient $r=0.94$, $p<0.001$) but that there are small differences (mean absolute difference of 1.1 mmol/l, with 5% of the data having differences >1.74 mmol/l). The question is whether these differences are acceptable or, in other words, whether these differences would lead to differences in treatment strategies. To answer this question we determined the concordance of the data after classification into hypoglycaemic, normoglycaemic or hyperglycaemic range since glucose values in these ranges require different treatment. Almost eighty percent of the data pairs were concordant. Of the errors made, 81% was in the hypoglycaemic range. This finding is in concordance with previous studies that have shown that the performance of the CGMS in the hypoglycaemic range is not always satisfactory.[5,6,10,11] Over- and underestimation of duration and severity of hypoglycaemic episodes have both been reported.[5,6,10,11] Of the previous two studies observing the reproducibility of the CGMS,[4,7] only Metzger *et al.*[4] clinically interpreted the data. They found that clinical interpretations were concordant for only 65% of the readings of simultaneously used CGMS devices. Unfortunately, their analysis of the glucose range in which the clinically significant errors were made, was not comparable to that in our study. Secondly, in that study a complete 24-hour recording was obtained in only half the study group, which suggests technical problems associated with the use of the CGMS.

The CGMS measures glucose levels in the interstitial fluid. The glucose concentration in the interstitial fluid is dependent on diffusion of glucose from peripheral capillaries. Theoretically, the differences found in this study may be attributed to differences in distance (and thus diffusion time) between the CGMS sensor electrode and the capillaries in the abdominal interstitial tissue. However, if that were the case, one of the two CGMS devices would constantly measure lower or higher glucose levels than the other CGMS device. Close inspection of the glucose profiles shown in *Figure 1*, however, shows that the glucose levels measured with the CGMS on the left and on the right side of the abdomen alternate with sometimes one and sometimes the other giving higher values. Hence, the cause of the differences in simultaneously measured CGMS glucose levels is most likely technical (the generation and measurement of electrical potential created by the reaction of glucose oxidase with glucose) or analytical (conversion of the electrical readings into glucose levels).

The manufacturers indications for use of the CGMS state that the device is currently intended for occasional use and that it should be used as a supplement to and not as a replacement for standard fingerstick measurements. The device is not intended to change insulin dosages based on the numbers generated. The CGMS identifies patterns of glucose fluctuations and this information should be used to adjust insulin administration patterns, change the patient's diet or improve the educational efforts.[12,17] The results of the present study show that reproducibility of the device in pregnant women with type 1 diabetes is adequate and this indicates that the CGMS is a useful tool in the management of type 1 diabetes in pregnant women. However, the CGMS should only be used as a supplementary method of daily glucose level measurement as a small degree of error, mainly in the hypoglycaemic range, is present.

References

1. Gold AE, Reilly R, Little J, Walker JD. The effect of glycemic control in the pre-conception period and early pregnancy on birth weight in women with IDDM. *Diabetes Care* 1998;21:535-538.
2. Kitzmiller JL, Buchanan TA, Kjos S, Combs CA, Ratner RE. Pre-conception care of diabetes, congenital malformations, and spontaneous abortions. *Diabetes Care* 1996;19:514-541.
3. Goldman JA, Dicker D, Feldberg D, Yeshaya A, Samuel N, Karp M. Pregnancy outcome in patients with insulin-dependent diabetes mellitus with preconceptional diabetic control: a comparative study. *Am J Obstet Gynecol* 1986;155:293-297.
4. Metzger M, Leibowitz G, Wainstein J, Glaser B, Raz I. Reproducibility of glucose measurements using the glucose sensor. *Diabetes Care* 2002;25:1185-1191.
5. McGowan K, Thomas W, Moran A. Spurious reporting of nocturnal hypoglycemia by CGMS in patients with tightly controlled type 1 diabetes. *Diabetes Care* 2002;25:1499-1503.
6. Caplin NJ, O'Leary P, Bulsara M, Davis EA, Jones TW. Subcutaneous glucose sensor values closely parallel blood glucose during insulin-induced hypoglycaemia. *Diabet Med* 2003;20:238-241.
7. Guerci B, Floriot M, Bohme P, Durain D, Benichou M, Jellimann S, Drouin P. Clinical Performance of CGMS in Type 1 Diabetic Patients Treated by Continuous Subcutaneous Insulin Infusion Using Insulin Analogs. *Diabetes Care* 2003;26:582-589.
8. Djakoure-Platonoff C, Radermercker R, Reach G, Slama G, Selam JI. Accuracy of the continuous glucose monitoring system in inpatient and outpatient conditions. *Diabetes Metab* 2003;29:159-162.
9. Sachedina N, Pickup JC. Performance assessment of the Medtronic-MiniMed Continuous Glucose Monitoring System and its use for measurement of glycaemic control in Type 1 diabetic subjects. *Diabet Med* 2003;20:1012-1015.
10. Accuracy of the GlucoWatch G2 Biographer and the continuous glucose monitoring system during hypoglycemia: experience of the Diabetes Research in Children Network. *Diabetes Care* 2004;27:722-726.
11. Kerssen A, de Valk HW, Visser GHA. The Continuous Glucose Monitoring System during pregnancy of women with type 1 diabetes mellitus; accuracy assesment. *Diabetes Technol Ther* 2004;6:645-651.

12. Mastrototaro J. The MiniMed Continuous Glucose Monitoring System (CGMS). *J Pediatr Endocrinol Metab* 1999;12 Suppl 3:751-758.

13. ADA. Clinical practice recommendations 1996. *Diabetes Care* 1996;19 Suppl 1:S1-118.

14. Bland JM, Altman DG. Comparing two methods of clinical measurement: a personal history. *Int J Epidemiol* 1995;24 Suppl 1:S7-14.

15. Diabetes mellitus. Report of a WHO Study Group. *World Health Organ Tech Rep Ser* 1985;727:1-113.

16. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;15:539-553.

17. Summary of safety and effectiveness data for the MiniMed Continuous Glucose Monitoring System (CGMS), 1999. *Available from http://www.fda.gov/cdrh/pdf/p98022.html.*

4

Diurnal glucose profiles during pregnancy in non-diabetic women

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Abstract

Objective Normoglycaemia during pregnancy in non-diabetic women has not yet been defined adequately. This study was aimed at observing diurnal glucose profiles in the home setting in each trimester of pregnancy and after pregnancy in non-diabetic women using the Continuous Glucose Monitoring System (CGMS).

Methods Twelve healthy non-diabetic pregnant women were asked to use the CGMS once during each trimester of pregnancy and once after the pregnancy. Diurnal glucose profiles were compared between the three trimesters of pregnancy and the non-pregnant state. Of each measurement day fasting glucose and post-prandial (breakfast, lunch and supper) peak glucose values were determined.

Results Nighttime glucose levels were lower during pregnancy, especially during the third trimester of pregnancy. Median fasting glucose values decreased from 4.2±0.6 mmol/l in the non-pregnant state to 3.3±1.5 mmol/l in the third trimester of pregnancy. Post-breakfast peak glucose values increased during pregnancy.

Conclusion This is the first study in which glucose profiles were measured continuously in the home setting in non-diabetic women in each trimester of the pregnancy and in the non-pregnant state. Nocturnal and fasting glucose levels decreased throughout pregnancy and were regularly less than the lower limit of normoglycaemia (3.9 mmol/l). Post-prandial glucose values increased during pregnancy and regularly exceeded the upper limit of normoglycaemia (7.8 mmol/l). These findings may be of help in establishing the aim of treatment strategies in pregnant women with diabetes mellitus and in diagnosing gestational diabetes.

Introduction

Pregnancies of women with type 1 diabetes mellitus are associated with increased perinatal and maternal morbidity.[1-5] Treatment in these women is aimed at 'achieving pregnancy outcomes that approximate that of the non-diabetic women'.[6] It is generally believed that this target can only be achieved when the diurnal glucose profiles of pregnant diabetics mimic that of pregnant women without diabetes.[7-9] Extensive research into the mechanisms responsible for the glucose homeostasis during pregnancy indicates that in healthy women late pregnancy may mimic a diabetogenic state.[10-13] However, it has proved difficult to establish the actual diurnal glucose profiles in pregnant non-diabetic women. Available studies are often limited to the second half of pregnancy [14,15] and the numbers of studied subjects are small.[16,17] Another obstacle has been the lack of possibilities for continuous glucose monitoring in the home setting.[15] The measurement of glucose levels in the subcutaneous interstitial tissue fluid is a new approach and allows continuous measurement of glucose levels in the home setting. It was the aim of this study to assess the diurnal glucose profiles of healthy women in each trimester of the pregnancy using the Continuous Glucose Monitoring System (CGMS).

Materials and methods

The Continuous Glucose Monitoring System

The Continuous Glucose Monitoring System (CGMS) is a device that measures glucose levels in the extracellular fluid of the abdominal subcutaneous tissue and stores measured values in a range of 2.2-22.2 mmol/l every five minutes during a 72 hour period. The CGMS consists of three components: a sterile disposable glucose sensor, a glucose monitor and a connecting cable. The sensor consists of a thin, one centimetre long flexible polyurethane tube that houses the glucose-sensing electrode. The sensor measures interstitial glucose as an electrical potential created by the reaction of glucose oxidase with glucose. The sensor signal is acquired every ten seconds and an average of the acquired signals is saved in the monitor every five minutes, providing 288 readings in 24 hours. Besides interstitial glucose levels, the monitor can store event markers for meals, insulin injections and exercise.
The electrical readings acquired by the sensor are converted into glucose levels (mmol/l) when the data are downloaded from the monitor to a personal computer. To calibrate the device, at least four fingerstick blood glucose levels have to be entered into the monitor every 24 hours. 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 day, 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]

Patients and Methods

Twelve healthy non-diabetic pregnant women whose BMI was less than 25 kg/m^2, who had no family history of diabetes and who had a singleton pregnancy were recruited for this study.[19] All subjects gave written informed consent before entering the study.

Each woman was asked to use the CGMS three times during the pregnancy (between 10 and 12 weeks, between 24 and 28 weeks and between 34 and 36 weeks of gestation) and at least three months after delivery and after they had stopped breastfeeding. They were asked to perform four fingerstick blood glucose measurements daily during the use of the CGMS, preferably before each meal and at bedtime. The blood glucose levels were used for calibration of the CGMS. The women kept a diary of meals, physical activity and type of day (working or non-working day).

Analysis

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. To compare the diurnal profiles, the median glucose level for each hour of the day per trimester of pregnancy was calculated. Repeated measurement analysis was performed to test the difference in diurnal glucose profiles between the different trimesters of pregnancy and the non-pregnant state (SPSS Release 12.0.1, SPSS inc., Chicago, Illinois).

Of each measurement day the fasting glucose value was determined. The fasting glucose was defined as the glucose value at time of rising in the morning. For each meal the post-prandial peak glucose value and time to post-prandial peak was determined. Median and interquartile ranges of the fasting glucose and the post-prandial glucose values were calculated for each trimester of pregnancy and for the non-pregnant measurement. Peak glucose values were compared between the trimesters of the pregnancy and the non-pregnant state using the non-parametric Kruskal-Wallis Test.

$P<0.05$ was considered statistically significant.

Results

Ten of the twelve women used the CGMS three times during pregnancy. Two women were recruited after the first trimester and therefore used the CGMS only twice during pregnancy. Eight of the twelve women used the CGMS after pregnancy.

Median maternal age at the birth of the infant was 30.2±2.3 years (median ± interquartile range). Eight women were nulliparous and four women were in their second pregnancy. One woman was delivered by caesarean section because of a breech position of the foetus; the others had a spontaneous vaginal delivery. Median gestational age at birth was 40.3±1.3 weeks and median birth weight was 3560±478 grams. When birth weight was expressed as percentage of the population mean corrected for gender and gestational age, median birth weight percentage was 103±10%. Eight infants were male and four were female. All infants were healthy at and after birth.

In all women two 24-hour periods of CGMS recording of adequate quality could be obtained at the different occasions. Analysis was therefore performed on the 48 hours of each CGMS measurement that best met the accuracy criteria.

The median diurnal glucose profiles are shown in *Figure 1* and the median glucose values are shown in *Table 1* and *Figure 2*. Two diurnal glucose profiles are shown in *Figure 3*. The most obvious changes during pregnancy were a lowering of nocturnal and fasting glucose levels, with lowest values occurring in the third trimester. The median fasting glucose value was 4.2 mmol/l in the non-pregnant state and 3.6, 3.4 and 3.3, respectively, in the three trimesters of pregnancy. During pregnancy fasting glucose levels could be as low as 2.2 mmol/l. The differences were not statistically significant, despite the observed trends. During the daytime there were no differences between the non-pregnant and pregnant state, apart from a higher post-breakfast glucose peak during the second and third trimester. The third trimester value was significantly higher than the values found during the other moments of observation ($p<0.001$). The median post-prandial peak time did not change in pregnancy (*Table 1*).

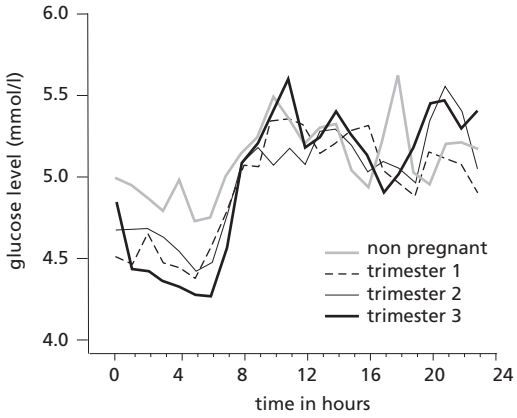

Figure 1. Median diurnal glucose profiles (midnight to midnight) of healthy women during and after pregnancy.

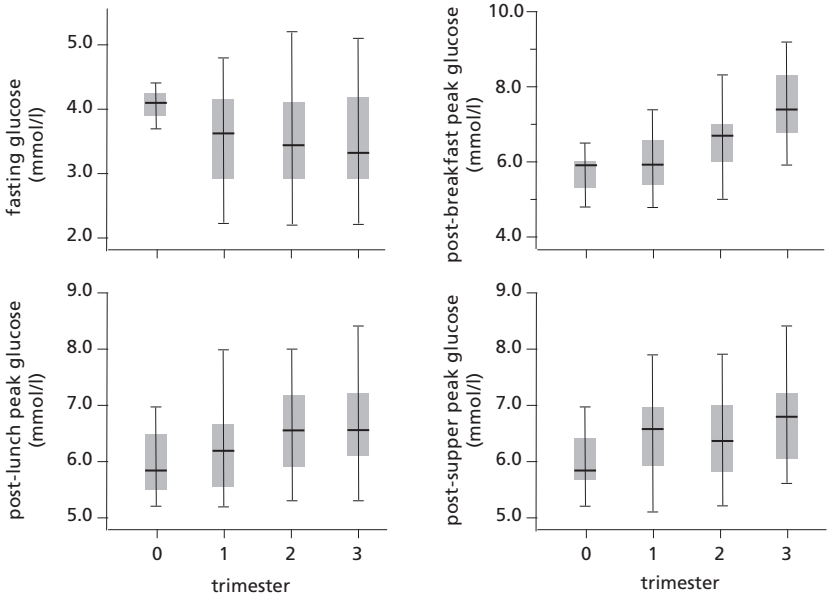

Figure 2. Meal-time glucose levels (median, interquartile range, range) during and after pregnancy in non-diabetic women.

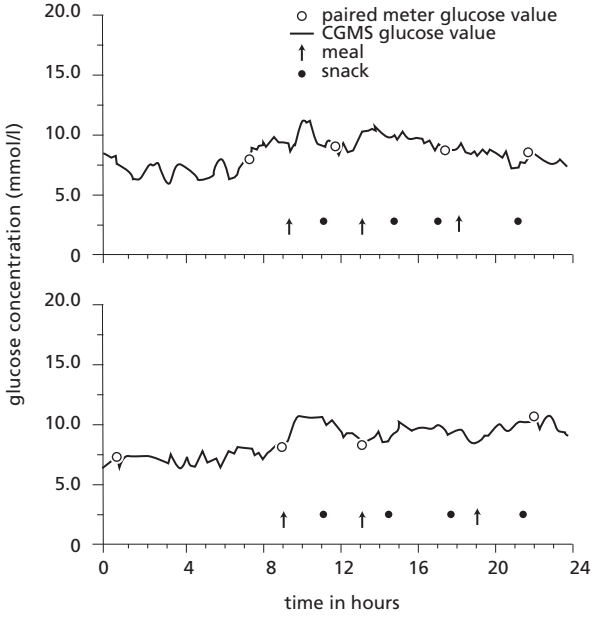

Figure 3. Twenty-four hour glucose profile of two non-diabetic pregnant women in the third trimester of pregnancy.

Table 1. Mealtime glucose profiles during and after pregnancy in non-diabetic women

Variable	Measure				Significance
	non-pregnant	first trimester	second trimester	third trimester	p
Subjects (n)	8	10	12	12	
Gestational age (weeks)	-	11.4 ± 2.0	25.2 ± 1.9	35.0 ± 1.4	
Analyzed meals (n)	48	54	72	66	
Median glucose level over 24 hours (mmol/l)*	4.9 ± 0.3 (4.6-5.3)	4.9 ± 0.5 (3.8-5.5)	5.0 ± 0.5 (3.8-5.9)	4.9 ± 0.6 (3.4-5.6)	0.967
Fasting glucose level (mmol/l)*	4.2 ± 0.6 (3.3-4.4)	3.6 ± 1.2 (2.2-4.8)	3.4 ± 1.3 (2.2-5.2)	3.3 ± 1.5 (2.2-5.1)	0.138
Post-breakfast peak glucose value (mmol/l)*	5.9 ± 0.8 (4.8-7.3)	5.9 ± 1.4 (4.8-7.4)	6.7 ± 1.0 (5.0-8.3)	7.4 ± 1.7‡ (5.9-9.2)	0.000
Post-breakfast peak time (min)†	59 ± 23	64 ± 20	56 ± 22	62 ± 24	0.394
Post-lunch peak glucose value (mmol/l)*	5.7 ± 1.1 (5.2-7.0)	6.2 ± 1.4 (5.2-8.0)	6.5 ± 1.3 (5.3-8.0)	6.6 ± 1.2 (5.3-8.4)	0.168
Post-lunch peak time (min)†	67 ± 16	63 ± 24	67 ± 24	75 ± 29	0.746
Post-supper peak glucose value (mmol/l)*	5.8 ± 1.0 (5.2-7.6)	6.6 ± 1.1 (5.1-7.9)	6.4 ± 1.4 (5.2-7.9)	6.8 ± 1.2 (5.6-8.4)	0.139
Post-supper peak time (min)†	75 ± 32	72 ± 27	80 ± 29	72 ± 24	0.687

* median ± interquartile range (range)

† median ± interquartile range

‡ significant with p<0.001, Kruskal-Wallis Test.

Discussion

This is the first study in which glucose profiles were measured continuously in the home setting in non-diabetic women during each trimester of pregnancy and in the non-pregnant state. Nocturnal and fasting glucose levels decreased during pregnancy and regularly fell below the accepted lower limit of normoglycaemia (3.9 mmol/l,[20]). Post-breakfast glucose values increased in the course of pregnancy and regularly exceeded the upper level of normoglycaemia (7.8 mmol/l,[21]). Most of the observed changes were not statistically significant, which may be due to the limited power of the study. It was difficult to recruit healthy subjects for this study.
In pregnant women with type 1 diabetes mellitus we have validated the CGMS with fingerstick blood glucose measurements and found a good correlation (r=0.94, p<0.001).[22] The glucose values given by the CGMS are calculated in retrospect using a regression analysis of blood glucose values with corresponding CGMS sensor readings.[18] The regression coefficient calculated in the calibration is strongly influenced by variations in the blood glucose values and becomes more accurate when the range of these values rises. Pregnancies of women with type 1 diabetes are complicated by large within-day glucose variability.[23] It is possible that the CGMS is less accurate in a non-diabetic population since glucose variability is generally

lower in these subjects. In case the absolute glucose values obtained with the CGMS may not be considered completely accurate, than the trends observed during pregnancy may still be considered the most important finding of our study. In healthy pregnant women, the first trimester of pregnancy is associated with an increase in insulin release by the ß-cells of the pancreas while insulin sensitivity (peripheral and hepatic) is unchanged. This may lead to a slight improvement in glucose tolerance.[12,13] In the second trimester of pregnancy, glucose stimulated insulin release increases further while peripheral insulin sensitivity begins to decline.[12,13] The third trimester of pregnancy is characterised by a 50% decrease in peripheral insulin sensitivity while there is a 3 to 3.5 fold increase in glucose mediated insulin response compared to the first trimester.[10,12,13] This leads to a decrease in glucose tolerance in late normal pregnancy. The increased maternal post-prandial glucose levels as found in this trimester are thought to be needed to compensate for the increasing glucose needs of the growing fetus.[11,24] Our study indeed showed a significant rise in post-prandial peak glucose values after breakfast throughout pregnancy. This pattern, however, was less clear after lunch and supper. In patients with diabetes there is an early morning decrease in glucose tolerance, the so-called 'dawn phenomenon'. This can be attributed to a sleep associated fall in hepatic glucose output (often leading to nocturnal hypoglycaemia) with a return to basal production rates on arousal combined with an increase in insulin resistance due to the physiological morning cortisol rise.[25,26] It is likely that during pregnancy in healthy women, the decrease in insulin sensitivity associated with normal pregnancy combined with the increase in insulin resistance induced by elevated early morning cortisol levels, leads to a dawn phenomenon-like effect as seen in diabetic patients. This would explain why the rise in post-prandial peak glucose values is greater after breakfast than after lunch and supper. The observed rise in post-prandial peak glucose values is obscured in the graph of the diurnal glucose profiles (*Figure 1*) because meals were not taken at standardised moments.

We found nocturnal and fasting glucose levels to decrease during pregnancy. This finding is in accordance with two previous studies in which lower fasting glucose levels in the second and third trimester of pregnancy were found.[15,27] This decrease is probably due to the fact that late pregnancy can be considered a catabolic condition.[28] Under this condition, liver glycogen stores are depleted and therefore gluconeogenesis is enhanced.[29] This, combined with an increased utilization of glucose, leads to hypoglycaemia, which is especially manifest after a period of fasting (nighttime).[30,31] During daytime such a decrease in glucose levels can be avoided by the frequent intake of food (*Figure 3*).

Our findings may be of help in establishing the aim of treatment strategies in pregnant women with diabetes mellitus and in diagnosing gestational diabetes. Incidental fall of glucose values below the lower limit of normoglycaemia, especially during the night, and values that exceed the upper limit of normoglycaemia,

especially after breakfast in the third trimester of pregnancy, appear to be a normal phenomenon in healthy women.

References

1. 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* 1997;315:275-278.
2. Evers IM, de Valk HW, Visser GHA. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. *BMJ* 2004;328:915.
3. 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* 1997;315:279-281.
4. 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* 2002;19:216-220.
5. Penney GC, Mair G, Pearson DW. Outcomes of pregnancies in women with type 1 diabetes in Scotland: a national population-based study. *BJOG* 2003;110:315-318.
6. Diabetes care and research in Europe: the Saint Vincent declaration. *Diabet Med* 1990;7:360.
7. Goldman JA, Dicker D, Feldberg D, Yeshaya A, Samuel N, Karp M. Pregnancy outcome in patients with insulin-dependent diabetes mellitus with preconceptional diabetic control: a comparative study. *Am J Obstet Gynecol* 1986;155:293-297.
8. 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* 1987;156:1089-1095.
9. Page RC, Kirk BA, Fay T, Wilcox M, Hosking DJ, Jeffcoate WJ. Is macrosomia associated with poor glycaemic control in diabetic pregnancy? *Diabet Med* 1996;13:170-174.
10. Buchanan TA, Metzger BE, Freinkel N, Bergman RN. Insulin sensitivity and B-cell responsiveness to glucose during late pregnancy in lean and moderately obese women with normal glucose tolerance or mild gestational diabetes. *Am J Obstet Gynecol* 1990;162:1008-1014.
11. Homko CJ, Sivan E, Reece EA, Boden G. Fuel metabolism during pregnancy. *Semin Reprod Endocrinol* 1999;17:119-125.
12. Catalano PM, Tyzbir ED, Wolfe RR, Calles J, Roman NM, Amini SB, Sims EA. Carbohydrate metabolism during pregnancy in control subjects and women with gestational diabetes. *Am J Physiol* 1993;264:E60-67.
13. Catalano PM, Tyzbir ED, Roman NM, Amini SB, Sims EA. Longitudinal changes in insulin release and insulin resistance in nonobese pregnant women. *Am J Obstet Gynecol* 1991;165:1667-1672.
14. Yogev Y, Ben-Haroush A, Chen R, Rosenn B, Hod M, Langer O. Diurnal glycemic profile in obese and normal weight nondiabetic pregnant women. *Am J Obstet Gynecol* 2004;191:949-953.
15. Parretti E, Mecacci F, Papini M, Cioni R, Carignani L, Mignosa M, La Torre P, Mello G. Third-trimester maternal glucose levels from diurnal profiles in nondiabetic pregnancies: correlation with sonographic parameters of fetal growth. *Diabetes Care* 2001;24:1319-1323.
16. Fraser RB, Ford FA, Milner RD. A controlled trial of a high dietary fibre intake in pregnancy--effects on plasma glucose and insulin levels. *Diabetologia* 1983;25:238-241.

17. Fraser R. Third trimester maternal glucose levels from diurnal profiles in nondiabetic pregnancies: correlation with sonographic parameters of fetal growth: a response to Parretti et al. and Jovanovic. *Diabetes Care* 2002;25:1104; author reply 1104-1106.
18. Mastrototaro J. The MiniMed Continuous Glucose Monitoring System (CGMS). *J Pediatr Endocrinol Metab* 1999;12 Suppl 3:751-758.
19. Gestational diabetes mellitus. *Diabetes Care* 2004;27 Suppl 1:S88-90.
20. Diabetes mellitus. Report of a WHO Study Group. *World Health Organ Tech Rep Ser* 1985;727:1-113.
21. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;15:539-553.
22. Kerssen A, de Valk HW, Visser GHA. The Continuous Glucose Monitoring System during pregnancy of women with Type 1 diabetes mellitus; accuracy assesment. *Diabetes Technol Ther* 2004;6:645-651.
23. Kerssen A, Evers IM, Valk de 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* 2003;13:309-313.
24. Chiasson JL, el Achkar GG, Ducros F, Bourque J, Maheux P. Glucose turnover and gluconeogenesis during pregnancy in women with and without insulin-dependent diabetes mellitus. *Clin Invest Med* 1997;20:140-151.
25. Blackard WG, Barlascini CO, Clore JN, Nestler JE. Morning insulin requirements. Critique of dawn and meal phenomena. *Diabetes* 1989;38:273-277.
26. De Feo P, Perriello G, Bolli GB. Somogyi and dawn phenomena: mechanisms. *Diabetes Metab Rev* 1988;4:31-49.
27. Cousins L, Rigg L, Hollingsworth D, Brink G, Aurand J, Yen SS. The 24-hour excursion and diurnal rhythm of glucose, insulin, and C-peptide in normal pregnancy. *Am J Obstet Gynecol* 1980;136:483-488.
28. Herrera E. Metabolic adaptations in pregnancy and their implications for the availability of substrates to the fetus. *Eur J Clin Nutr* 2000;54 Suppl 1:S47-51.
29. Assel B, Rossi K, Kalhan S. Glucose metabolism during fasting through human pregnancy: comparison of tracer method with respiratory calorimetry. *Am J Physiol* 1993;265:E351-356.
30. Bleicher SJ, O'Sullivan JB, Freinkel N. Carbohydrate Metabolism in Pregnancy. V. The Interrelations of Glucose, Insulin and Free Fatty Acids in Late Pregnancy and Post Partum. *N Engl J Med* 1964;271:866-872.
31. Herrera E, Knopp RH, Freinkel N. Carbohydrate metabolism in pregnancy. VI. Plasma fuels, insulin, liver composition, gluconeogenesis, and nitrogen metabolism during late gestation in the fed and fasted rat. *J Clin Invest* 1969;48:2260-2272.

5

Poor glucose control in women with type 1 diabetes mellitus and 'safe' HbA_{1c}-values in the first trimester of pregnancy

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Abstract

Objective To observe glycaemic excursions, measured continuously over 24 hours, in relation to HbA_{1c}-levels in the first trimester of pregnancy of women with type 1 diabetes mellitus.

Methods The MiniMed Continuous Glucose Monitoring System (CGMS) was used to obtain glucose values every five minutes during 24 hours. HbA_{1c}-level was determined at the end of the continuous glucose recording and six to 12 weeks after the continuous glucose recording.

Results Continuous glucose recordings were obtained in 13 women between seven and 15 weeks of gestation. Nine patients had HbA_{1c}-levels ≤7.0% (≤1% above the upper limit of normal range, ADA) while up to 41.3% of the readings had values ≤3.9 mmol/l (70 mg/dl) and up to 52.8% of the readings had values ≥7.8 mmol/l (140 mg/dl).

Conclusions HbA_{1c}-level does not reflect the complexities of glycaemic control in women with type 1 diabetes who are considered having accomplished tight glycaemic control in the first trimester of pregnancy.

Introduction

Over the last decades perinatal morbidity and mortality in pregnancies complicated by maternal type 1 diabetes mellitus have decreased significantly. However, a considerable risk of complications remains.[1] The American Diabetes Association states that in pregnancy tight glycaemic control is accomplished when HbA_{1c}-level is within 1% above the upper limit of the normal range (4.0-6.0%). It is assumed that HbA_{1c}-levels $\leq$7.0% are associated with rates of congenital malformations and macrosomia no greater than those in non-diabetic pregnancy.[2] However, several studies have shown that complications such as congenital malformations and fetal macrosomia still occur at a considerable higher frequency than in a healthy population also if HbA_{1c}-level is only slightly increased (6.0-7.0%).[3-6] This suggests that either HbA_{1c}-level does not sufficiently reflect the complexities of glycaemic control or that current criteria for strict glycaemic control are not 'safe'.
Conventional fingerstick self-measurements of glucose levels provide only snapshot images and symptomless or symptom-poor hyperglycaemia and hypoglycaemia at other time-points are missed. These silent abnormal glucose levels can be instrumental in causing fetal complications. Kyne-Grzebalski *et al.*[7] reported that the frequency of hyperglycaemia is underestimated in pregnant women who seem to be well controlled using home self-monitoring records and HbA_{1c}-levels.
Novel methods of continuous glucose measurement will help to improve insight in glycaemic control in diabetic pregnancy. The MiniMed Continuous Glucose Monitoring System (CGMS) is the latest advance in glucose monitoring and has revealed unexpected nocturnal hypoglycaemic episodes and marked increases in post-prandial glucose levels in non-pregnant diabetic patients with low HbA_{1c}-levels.[8-11]
The objective of this study was to use the CGMS to observe glycaemic excursions in women with type 1 diabetes mellitus in the first trimester of pregnancy.

Methods

Between November 2001 and November 2002, all 13 women with type 1 diabetes mellitus who visited our out-patient clinic and who were in the first trimester of their pregnancy were asked to participate in this study. Patients were asked to make a 72-hour continuous glucose recording using the CGMS. All recordings were made on regular weekdays and patients continued their normal daily activities. In all patients the CGMS was placed in the abdominal skin. While using the CGMS patients were asked to enter blood glucose values obtained through fingerstick measurements four times a day. These values were used for calibration sensitivity checks of the CGMS. HbA_{1c}-level was determined at the end of the continuous glucose recording and six to 12 weeks after the continuous glucose recording.

The CGMS measures glucose levels in the extracellular fluid of the subcutaneous tissue. Clinical studies have shown that subcutaneous glucose measurements generally follow venous blood values and fingerstick glucose values.[12-16] The CGMS stores values within a range of 2.2-22.2 mmol/l (40-400mg/dl) every five minutes providing 288 readings in 24 hours.
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 day. 2) correlation coefficient between sensor glucose values and meter blood glucose readings ≥0.79. 3) average value of differences between sensor glucose values and meter glucose values for a given day ≤28%.

Results

Continuous glucose recordings were obtained in 13 women. Their mean age was 32 years (range 22-38) and mean duration of diabetes 14 years (range 2-23). One patient had a background retinopathy. Nine patients were treated with subcutaneous insulin infusion. Mean gestational age on the first day of the continuous glucose recording was 11 weeks (range 7-15). Mean HbA_{1c}-level measured at the end of the continuous glucose recording was 7.2% (range 5.3-9.9%). Mean HbA_{1c}-level six to12 weeks after the continuous glucose measurement was 6.7% (range 5.4-7.8%). All 13 patients had CGMS data of at least 24 successive hours that met the accuracy criteria and were therefore fit for analysis. Of the continuous glucose recordings that were longer than 24 hours, the readings of 24 successive hours that best met the accuracy criteria were used for this study. The recordings of the nine patients who had HbA_{1c}-levels ≤7.0% six to 12 weeks after the glucose recording are shown in *Figure 1*, and are ordered according to HbA_{1c}-level (patient 1 has the lowest HbA_{1c}, patient 9 has the highest HbA_{1c}-level).
Between 0 and 41.3% of the readings had glucose values ≤3.9 mmol/l (70 mg/dl) and between 0 and 52.8% of the readings had glucose values ≥7.8 mmol/l (140 mg/dl). Neither the percentage of readings ≤3.9 mmol/l (r=0.18, NS) nor that ≥7.8 mmol/l (r=0.02, NS) were significantly related to the HbA_{1c}-level obtained six to 12 weeks after the glucose recording, *Figure 2*. The correlation coefficient between HbA_{1c}-level and median glucose value was -0.018 (NS). Correlation of readings ≤3.9 mmol/l, percentage of readings ≥7.8 mmol/l and median glucose value with HbA_{1c}-level obtained at the time of the continuous glucose recording, showed similar non-significant values (-0.20, 0.065 and 0.066, respectively).
Nine of the 13 patients had HbA_{1c}-levels ≤7.0% (measured six to 12 weeks after the glucose recording). Of these patients only patient 1 had accomplished strict glycaemic control according to the continuous glucose measurement (mean 4.2, SD 0.2, range 3.6-4.9 mmol/l), fingerstick blood glucose measurements (mean 3.9, SD 0.6, range 3.3-4.8 mmol/l) and HbA_{1c} (5.4%). She did not have any hyperglycaemic

episodes during the continuous glucose recording but 17.4% of the readings showed values ≤3.9 mmol/l. In patients 2 to 9 HbA_{1c} ranged from 6.0% to 7.0%, percentage of readings ≤3.9 mmol/l ranged from 0 to 36.1% and percentage of readings ≥7.8 mmol/l ranged from 17.0 to 61.1%. Visual inspection of the glucose excursions of these women shows that glucose control was far from perfect.

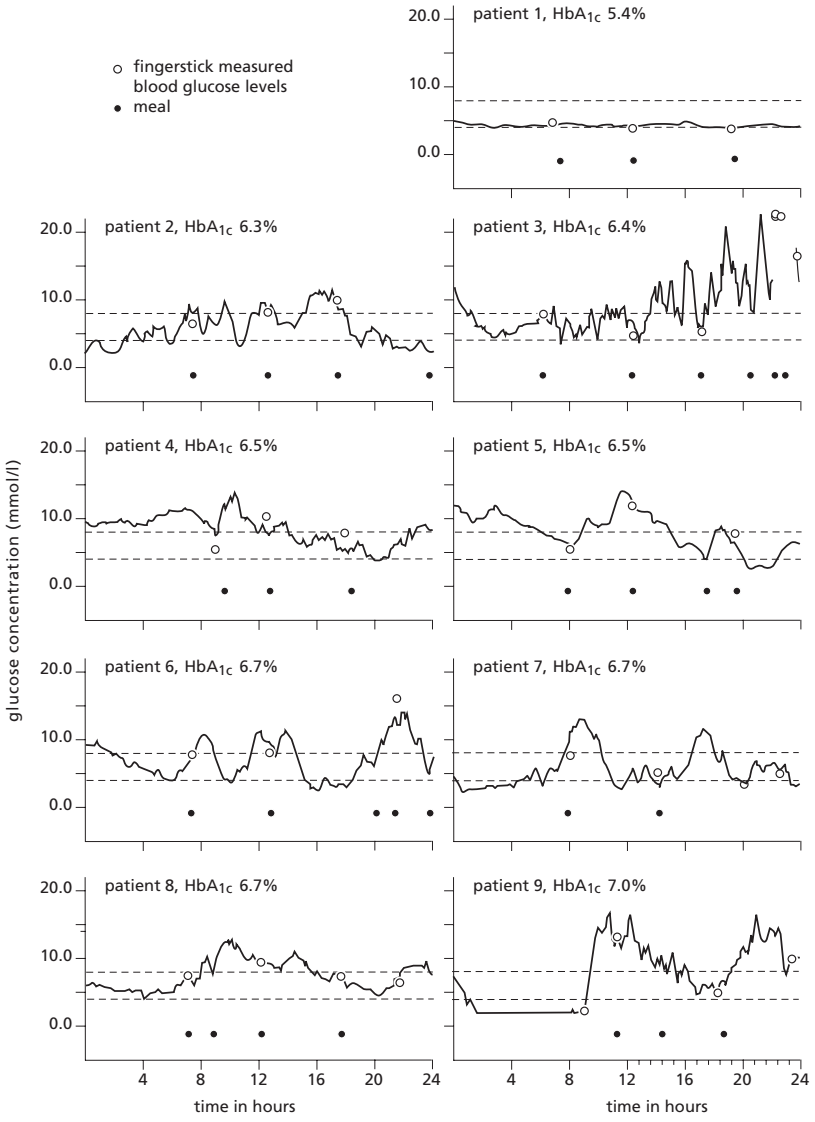


Figure 1. Twenty-four hour glucose excursion and HbA_{1c} measured 6-12 weeks after continuous glucose registration.

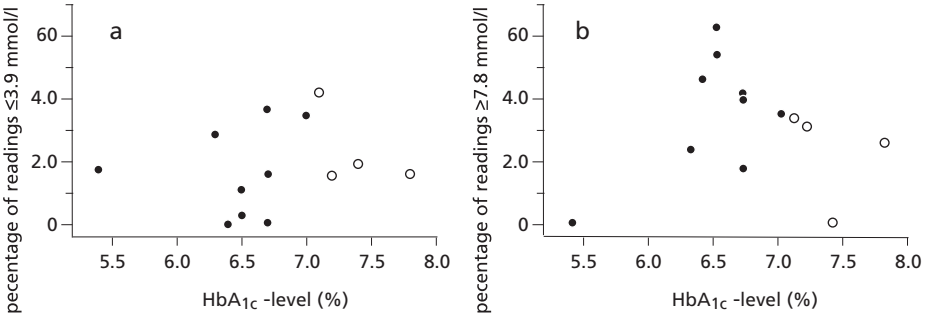


Figure 2. Relationship between HbA_{1c}-level and a) percentage of readings ≤3.9 mmol/l and b) percentage of readings ≥7.8 mmol/l of patients with HbA_{1c}-level ≤7.0% (•) and patients with HbA_{1c}-level >7.0% (○).

Discussion

This study demonstrates that HbA_{1c}-level does not reflect the complexities of glycaemic control in women with type 1 diabetes who are considered having accomplished tight glycaemic control in the first trimester of pregnancy. These data indicate that tight glycaemic control may only be accomplished when HbA_{1c} -level is ≤ 6.0% and that there is considerable glucose variability in the HbA_{1c} range of 6.0-7.0% (≤1% above the upper limit of normal range), the latter still considered to be part of the 'safe' range. We did not find a straightforward relation between HbA_{1c} -level and percentage of hypoglycaemic or hyperglycaemic readings. This may be explained by the fact that only one 24-hour recording was compared to a measure of long term diabetic control (HbA_{1c}-level). Kyne-Grzebalski *et al.*[7] demonstrated a positive relation between HbA_{1c}-level and percentage of glucose measurements out of range (both hyperglycaemia and hypoglycaemia) in a study in which glucose measurements were taken over a long period (>16 weeks) in pregnancy. These data may, on the other hand, be biased since glucose measurements were not standardised over the day.

Our data indicate that the target and 'safe' HbA_{1c}-range during the first trimester of pregnancy should be ≤6.0%. However, the price to pay for tight glycaemic control is severe (nocturnal) hypoglycaemia. The correlation between HbA_{1c}-level and frequency of clinically detected hypoglycaemia has been shown in several studies.[17,18] Hypoglycaemia during the first trimester of pregnancy is seen with a prevalence of 37-41%.[19,20] Patient 9 illustrates an asymptomatic long-lasting nocturnal hypoglycaemia and the effect on subsequent glucose excursion. As the CGMS does not record glucose levels <2.2 mmol/l it is not possible to determine the exact biochemical severity of the hypoglycaemia. Apart from the

possible effects on the mother, hypoglycaemia and subsequent hyperglycaemia contributes to glucose variability and to embryopathic risk. At the same time a direct teratogenic effect of hypoglycaemia cannot be excluded.[21]
In conclusion, this study shows that HbA_{1c}-values in the range currently considered to be safe with regard to pregnancy outcome does not sufficiently reflect the complexities of glycaemic control. Further research is needed to evaluate whether the recommended target HbA_{1c}-level during pregnancy should be lowered to 6.0% or whether HbA_{1c}-level is not an accurate tool for the monitoring of glucose regulation of type 1 diabetes in women during the first trimester of pregnancy and should therefore be dismissed.

References

1. 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* 1997;315:275-278.
2. Preconception care of women with diabetes. *Diabetes Care* 2003;26 Suppl 1:S91-93.
3. Evers IM, Bos AM, Aalders AL, van Ballegooie E, de Valk HW, van Doormaal JJ, ter Brugge HG, Visser GHA. [Pregnancy in women with diabetes mellitus type I: maternal and perinatal complications, in spite of good blood glucose control]. *Ned Tijdschr Geneeskd* 2000;144:804-809.
4. 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* 1996;103:427-433.
5. Knight G, Worth RC, Ward JD. Macrosomy despite a well-controlled diabetic pregnancy. *Lancet* 1983;2:1431.
6. 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* 2002;45:1484-1489.
7. 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* 1999;16:702-706.
8. Bode BW, Gross TM, Thornton KR, Mastrototaro JJ. Continuous glucose monitoring used to adjust diabetes therapy improves glycosylated hemoglobin: a pilot study. *Diabetes Res Clin Pract* 1999;46:183-190.
9. Chase HP, Kim LM, Owen SL, MacKenzie TA, Klingensmith GJ, Murtfeldt R, Garg SK. Continuous subcutaneous glucose monitoring in children with type 1 diabetes. *Pediatrics* 2001;107:222-226.
10. Kaufman FR. Role of the continuous glucose monitoring system in pediatric patients. *Diabetes Technol Ther* 2000;2 Suppl 1:S49-52.
11. Cheyne E, Kerr D. Making 'sense' of diabetes: using a continuous glucose sensor in clinical practice. *Diabetes Metab Res Rev* 2002;18 Suppl 1:S43-48.
12. Bantle JP, Thomas W. Glucose measurement in patients with diabetes mellitus with dermal interstitial fluid. *J Lab Clin Med* 1997;130:436-441.
13. Fischer U. Continuous in vivo monitoring in diabetes: the subcutaneous glucose concentration. *Acta Anaesthesiol Scand Suppl* 1995;104:21-29.

14. Johnson KW, Mastrototaro JJ, Howey DC, Brunelle RL, Burden-Brady PL, Bryan NA, Andrew CC, Rowe HM, Allen DJ, Noffke BW, et al. In vivo evaluation of an electroenzymatic glucose sensor implanted in subcutaneous tissue. *Biosens Bioelectron* 1992;7:709-714.

15. Sternberg F, Meyerhoff C, Mennel FJ, Bischof F, Pfeiffer EF. Subcutaneous glucose concentration in humans. Real estimation and continuous monitoring. *Diabetes Care* 1995;18:1266-1269.

16. Sternberg F, Meyerhoff C, Mennel FJ, Mayer H, Bischof F, Pfeiffer EF. Does fall in tissue glucose precede fall in blood glucose? *Diabetologia* 1996;39:609-612.

17. Kimmerle R, Heinemann L, Delecki A, Berger M. Severe hypoglycemia incidence and predisposing factors in 85 pregnancies of type I diabetic women. *Diabetes Care* 1992;15:1034-1037.

18. Bendtson I, Kverneland A, Pramming S, Binder C. Incidence of nocturnal hypoglycaemia in insulin-dependent diabetic patients on intensive therapy. *Acta Med Scand* 1988;223:543-548.

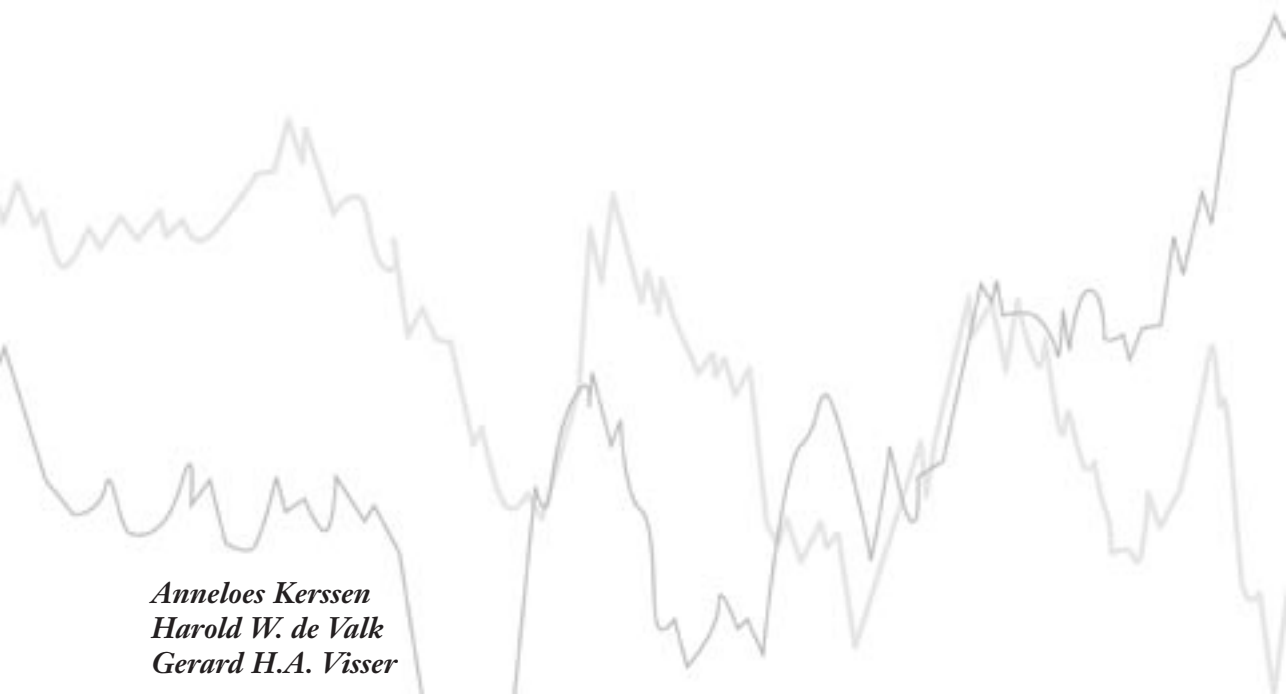
19. Hellmuth E, Damm P, Molsted-Pedersen L, Bendtson I. Prevalence of nocturnal hypoglycemia in first trimester of pregnancy in patients with insulin treated diabetes mellitus. *Acta Obstet Gynecol Scand* 2000;79:958-962.

20. Evers IM, ter Braak EW, de Valk HW, van Der Schoot B, Janssen N, Visser GHA. Risk indicators predictive for severe hypoglycemia during the first trimester of type 1 diabetic pregnancy. *Diabetes Care* 2002;25:554-559.

21. Braak ter EW, Evers IM, Willem Erkelens D, Visser GHA. Maternal hypoglycemia during pregnancy in type 1 diabetes: maternal and fetal consequences. *Diabetes Metab Res Rev* 2002;18:96-105.

6

Do HbA_{1c}-levels adequately reflect glycaemic control during pregnancy in women with type 1 diabetes mellitus?



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Abstract

Objective Pregnancies of women with type 1 diabetes mellitus are associated with increased rates of maternal and perinatal complications. These complication rates remain elevated despite the achievement of the treatment goals as described in the widely used guidelines of the American Diabetes Association (*i.e.* HbA_{1c}-level ≤7.0%). The aim of this study was to evaluate the accuracy of the limits of HbA_{1c}-levels currently used in these guidelines in relation to glycaemic control in pregnant women with type 1 diabetes. Secondly, the number of self-monitored blood glucose levels (SMBG) that have to be obtained daily to give an accurate idea of glucose levels in these women was assessed.

Methods Forty-three pregnant women with diabetes were asked to use the Continuous Glucose Monitoring System (CGMS) once in each trimester of pregnancy. Glucose levels measured with the CGMS were compared between patients with HbA_{1c}-levels 4.0-6.0%, 6.0-7.0% and >7.0%. Glucose levels measured with SMBG and the CGMS were compared between patients with 4-5, 6-9 and ≥10 SMBG daily.

Results In patients with HbA_{1c}-levels ≤6.0% the glucose levels were significantly better than in patients with HbA_{1c}-levels >6.0%. Glucose measures in women with HbA_{1c}-levels 6.0-7.0% and >7.0% did not differ. The detection rate of hyper- and hypoglycaemic episodes was significantly higher in patients with ≥10 SMBG compared to patients with <10 SMBG daily.

Conclusion Treatment of diabetes in pregnant women should be aimed at achieving HbA_{1c}-levels within the normal range. A minimum of ten SMBG is necessary to adequately obtain an image of all daily glucose fluctuations.

Introduction

Pregnancy in women with type 1 diabetes mellitus is associated with an increased incidence of perinatal and maternal complications.[1-6] It is generally assumed that complication rates decrease when glycaemic control during pregnancy is tightened.[7-9] The 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.[10] It is assumed that these HbA_{1c}-levels are associated with rates of congenital malformations and spontaneous abortions equal to those in healthy women.[10] However, several studies have shown that in patients with these 'acceptable' HbA_{1c}-levels, complication rates remain higher than in patients with normal HbA_{1c}-levels.[11,12] 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.

Currently, self-monitoring of blood glucose levels (SMBG) is the established and easiest way of observation of daily glucose levels in patients with diabetes. It is critical for the maintenance of diabetic control [13-16] and is a safe and effective way of managing diabetes.[17] 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 mellitus.[18] SMBG, however, has its limitations. In infants with diabetes it has been found that nocturnal hypoglycaemia and postprandial hyperglycaemia remain undetected when they are monitored routinely three to five times a day.[19] In non-pregnant adults true diurnal variability in glucose levels is too large to be accurately reflected by seven measurements a day.[20] With the increased complication rates in pregnancies of women with type 1 diabetes, accurate reflection of glucose levels is important.

A useful device for the measurement of glucose levels is the Continuous Glucose Monitoring System (CGMS). It is a portable device that measures glucose levels every five minutes uninterrupted for 72 hours. With this device ambulatory continuous glucose monitoring is possible while patients maintain their usual daily activities.

The aim of this study was to evaluate the accuracy of the limits of HbA_{1c}-levels during pregnancy currently used in international guidelines in relation to glycaemic control determined with the CGMS. Secondly, the number of SMBG that have to be obtained daily to give an accurate idea of glucose levels in pregnant women with type 1 diabetes mellitus was assessed.

Materials and methods

The Continuous Glucose Monitoring System

The Continuous Glucose Monitoring System (CGMS) measures glucose levels in the extracellular fluid of the abdominal subcutaneous tissue through electrochemical reaction of the glucose with glucose oxidase. The CGMS stores values within a range of 2.2-22.2 mmol/l (40-400mg/dl) every five minutes providing 288 readings in 24 hours. 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 enter data from at least four fingerstick glucose measurements each day for calibration of the system.

The data of the CGMS are considered valid if three criteria for optimal accuracy are met: 1) at least four paired sensor glucose / meter glucose readings per day; 2) correlation coefficient between sensor glucose values and meter blood glucose readings ≥ 0.79; 3) average value of differences between sensor glucose values and meter glucose values for a given day $\leq 28\%$.[21] It has been shown that the CGMS is an accurate tool for glucose monitoring in pregnant women with type 1 diabetes.[22] 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 hours were missing.

Methods

From December 2001 through June 2004 forty-three pregnant women with type 1 diabetes mellitus were recruited from the obstetrical out-patient clinic of the University Medical Centre, Utrecht, The Netherlands. All patients gave written informed consent and participated in the study. The patients were asked to use the CGMS once in each trimester of the pregnancy.

HbA_{1c}-levels were determined within one week after each continuous glucose measurement. In 55% of the patients, HbA_{1c}-levels were also obtained six to eight 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 one week or six to eight weeks after the CGMS measurement were not significantly different ($p>0.1$). HbA_{1c}-levels determined within one 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 per day that were used for the calibration of the CGMS. All SMBG were performed through fingerstick measurement and determined with the MediSense Precision Xtra glucose meter (Abbott, Bedford, MA 01730, USA).

Analysis

Glucose levels measured with the CGMS were expressed as mean and range per 24 hours. Hyperglycaemia was defined as glucose level ≥7.8 mmol/l and hypoglycaemia was defined as glucose level ≤3.9 mmol/l.[23,24] The number of hyper- and hypoglycaemic episodes per 24 hours measured with the CGMS were counted. Glucose variability of the glucose levels measured with the CGMS was expressed as coefficient of variance (CV=100 x SD/mean) and Mean Amplitude of Glycaemic Excursions (MAGE) over 24 hours. The MAGE is calculated by taking the arithmetic mean of the glucose increases or decreases when both ascending and descending segments exceed the value of one standard deviation of the mean glucose over a 24-hour period.[25]

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

The measurement days were categorized in three groups: 1) four to five SMBG daily; 2) six to nine SMBG daily; 3) ten or more SMBG daily. For each measurement day, the difference in mean glucose level and the difference in glucose range between SMBG and CGMS measurements and the hyper- and hypoglycaemia detection rate were calculated. The differences in mean glucose level and glucose range and the hyper- and hypoglycaemia detection rates were compared between the three groups using one-way ANOVA and post-hoc Bonferroni. For evaluation $p<0.05$ was considered significant.

Results

There were no adverse events 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. There were 68 measurement days in the first, 59 in the second and 58 in the third trimester of pregnancy. HbA_{1c}-levels ranged from 5.1 to 9.1%. 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 relationship between HbA_{1c}-levels and CGMS glucose values is shown in *Table 1* and *Table 2*. In patients with HbA_{1c}-levels ≤6.0% all but one of the glucose measures were significantly better than in patients with HbA_{1c}-levels of 6.0-7.0% or >7.0%. Only the number of hypoglycaemic episodes was significantly higher. Glucose measures in women with HbA_{1c}-levels 6.0-7.0% and >7.0% did not differ, apart from mean glucose and glucose range.

There were 92 measurement days during which blood glucose values were determined 4-5 times (Group 1). There were 70 measurement days on which blood

Table 1. Mean of mean glucose level, glucose range, number of hyper- and hypoglycaemic episodes, MAGE and CV per 24 hours of CGMS glucose levels in patients with HbA_{1c}-levels 4.0-6.0%. 6.0-7.0% and >7.0%.

	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
MAGE (mmol/l)	3.1	4.6	5.7
Coefficient of variance (%)	27	34	39

Table 2. Significance levels of comparison of mean glucose level, glucose range, number of hyper- and hypoglycaemic episodes, MAGE and CV per 24 hours of CGMS glucose levels between patients with HbA_{1c}-level 4.0-6.0%. 6.0-7.0% and >7.0%.

	Group A versus Group B	Group A versus Group C	Group B versus Group C
Mean glucose level	0.000*	0.000*	0.032*
Glucose range	0.000*	0.000*	0.029*
Hyperglycaemic episodes	0.000*	0.000*	0.691
Hypoglycaemic episodes	0.009*	0.031*	1.000
MAGE	0.000*	0.000*	0.065
Coefficient of Variance	0.001*	0.001*	0.420

Group A: HbA_{1c} 4.0-6.0%; Group B: HbA_{1c} 6.0-7.0%; Group C: HbA_{1c} >7.0%

glucose values were determined 6-9 times (Group 2) and there were 23 measurement days on which blood glucose values were determined ≥10 times (Group 3). Mean HbA_{1c} -levels did not differ significantly between the groups (6.5%, 6.3% and 6.2%, respectively). A comparison between mean glucose level, glucose range and number of hyper- and hypoglycaemic episodes measured with SMBG and the CGMS given in *Table 3*. Hyperglycaemia detection rate increased significantly with an increase of number of SMBG (*Table 4*). Hypoglycaemia detection rate was significantly higher in Group 3 as compared to Group 1 and Group 2 (*Table 4*). The mean glucose levels did not differ between SMBG groups.

Table 3. Mean glucose level, glucose range, number of hyper- and hypoglycaemic episodes and difference or detection rate per 24 hours of SMBG and CGMS in patients with 4-5, 6-9 and ≥10 SMBG.

	Number of SMBG								
	4-5			6-9			≥10		
	SMBG	CGMS	Difference or Detection rate	SMBG	CGMS	Difference or Detection rate	SMBG	CGMS	Difference or Detection rate
Mean glucose level (mmol/l)	6.8	6.9	0.07 mmol/l	6.5	6.3	-1.11 mmol/l	6.2	6.3	0.14 mmol/l
Glucose range (mmol/l)	5.1	9.6	4.53 mmol/l	6.4	8.1	1.75 mmol/l	7.8	8.9	1.11 mmol/l
Hyperglycaemic episodes (n)	1.2	3.4	35%	1.7	2.9	59%	1.8	1.8	100%
Hypoglycaemic episodes (n)	0.6	2.3	26%	1.2	2.5	48%	2.7	3.7	73%

Table 4. Significance levels of comparison of difference in mean glucose level and glucose range and hyper- and hypoglycaemia detection rate per 24 hours between patients with 4-5, 6-9 and ≥10 SMBG.

	Group 1 versus Group 2	Group 1 versus Group 3	Group 2 versus Group 3
Difference in mean glucose level	0.791	1.000	0.925
Difference in glucose range	0.000*	0.000*	1.000
Hyperglycaemia detection rate	0.002*	0.000*	0.015*
Hypoglycaemia detection rate	0.688	0.001*	0.021*

Group 1: 4-5 SMBG; Group 2: 6-9 SMBG; Group 3: ≥10 SMBG

* significant with $p<0.05$

Discussion

This study shows 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 is 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 widely used guidelines of the ADA stating that in pregnancy HbA_{1c}-levels within 1% above the upper limit of normal range are acceptable when treatment is aimed at achieving pregnancy outcomes comparable to those in the healthy population.[10] Although our data are purely biochemical and the relationship with pregnancy outcome was not assessed, the persisting high rates of complications that are seen in women with type 1 diabetes and HbA_{1c}-levels 6.0-7.0% [11,12,26] may be explained by our findings. It is generally assumed that hyperglycaemia during the first trimester is the cause of congenital malformations [1,27] while hyperglycaemia in the second and third trimester of pregnancy leads to macrosomia, neonatal hypoglycaemia or sudden intra-uterine death of the fetus.[28,29] Macrosomia is associated to complications at delivery such as shoulder dystocia or caesarean section.[30,31] Neonatal hypoglycaemia may cause behavioural and intellectual development problems in later life.[3,32] This enumeration of complications caused by hyperglycaemia emphasises the importance of the diagnosis, treatment and prevention of hyperglycaemic episodes. This study shows that hyperglycaemia detection rate increases (up to 100%) when patients measure themselves ten or more times daily.

Normalization of blood glucose levels in pregnant women with diabetes is associated with an increased risk of hypoglycaemic episodes.[33] This finding is confirmed in the present study as the number of hypoglycaemic episodes is increased when HbA_{1c}-levels are ≤6.0%. In women with type 1 diabetes, pregnancy per se is associated with an increased incidence of hypoglycaemic episodes, mainly in the

first trimester.[34-36] As hypoglycaemia can lead to loss of consciousness and even death, detection and treatment of hypoglycaemia is of great importance. Frequent SMBG improves the detection rate of hypoglycaemia when performed ten or more times daily. Detection rate, 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.[35,37] It is also conceivable that in case of symptomatic hypoglycaemia, patients will treat the hypoglycaemia before measuring their blood glucose level.
In summary, on the basis of these data the treatment of type 1 diabetes in pregnant women should be aimed at achieving HbA_{1c}-levels within the normal range. The price to pay for the improvement of HbA_{1c}-levels is an increase in the incidence of hypoglycaemic episodes. This is an important obstacle in the treatment of diabetes in pregnant women. Treatment should therefore be individualized and be aimed at finding a balance between glycaemic control and hypoglycaemia risk. In order to obtain an accurate impression of glucose profiles, patients should monitor themselves at least ten times per day, which may be difficult to achieve in clinical practise.

References

1. Cousins L. Congenital anomalies among infants of diabetic mothers. Etiology, prevention, prenatal diagnosis. *Am J Obstet Gynecol* 1983;147:333-338.
2. 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* 1997;315:275-278.
3. 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* 1997;315:279-281.
4. Dunne FP. Pregestational Diabetes Mellitus and Pregnancy. *Trends Endocrinol Metab* 1999;10:179-182.
5. Evers IM, Bos AM, Aalders AL, van Ballegooie E, de Valk HW, van Doormaal JJ, ter Brugge HG, Visser GHA. [Pregnancy in women with diabetes mellitus type I: maternal and perinatal complications, in spite of good blood glucose control]. *Ned Tijdschr Geneeskd* 2000;144:804-809.
6. Penney GC, Mair G, Pearson DW. Outcomes of pregnancies in women with type 1 diabetes in Scotland: a national population-based study. *BJOG* 2003;110:315-318.
7. Goldman JA, Dicker D, Feldberg D, Yeshaya A, Samuel N, Karp M. Pregnancy outcome in patients with insulin-dependent diabetes mellitus with preconceptional diabetic control: a comparative study. *Am J Obstet Gynecol* 1986;155:293-297.
8. 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* 1987;156:1089-1095.
9. Page RC, Kirk BA, Fay T, Wilcox M, Hosking DJ, Jeffcoate WJ. Is macrosomia associated with poor glycaemic control in diabetic pregnancy? *Diabet Med* 1996;13:170-174.
10. ADA. Preconception care of women with diabetes. *Diabetes Care* 2004;27 Suppl 1:S76-S78.
11. Evers IM, de Valk HW, Visser GHA. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. *BMJ* 2004;328:915.

12. Suhonen L, Hiilesmaa V, Teramo K. Glycaemic control during early pregnancy and fetal malformations in women with type I diabetes mellitus. *Diabetologia* 2000;43:79-82.

13. Walford S, Gale EA, Allison SP, Tattersall RB. Self-monitoring of blood-glucose. Improvement of diabetic control. *Lancet* 1978;1:732-735.

14. Schiffrin A, Belmonte M. Multiple daily self-glucose monitoring: its essential role in long-term glucose control in insulin-dependent diabetic patients treated with pump and multiple subcutaneous injections. *Diabetes Care* 1982;5:479-484.

15. Espersen T, Klebe JG. Self-monitoring of blood glucose in pregnant diabetics. A comparative study of the blood glucose level and course of pregnancy in pregnant diabetics on an out-patient regime before and after the introduction of methods for home analysis of blood glucose. *Acta Obstet Gynecol Scand* 1985;64:11-14.

16. Lam KS, Ma JT, Chan EY, Yeung RT. Sustained improvement in diabetic control on long-term self-monitoring of blood glucose. *Diabetes Res Clin Pract* 1986;2:165-171.

17. Heller SR, Lowe JM, Johnson IR, O'Brien PM, Clarke P, Symonds EM, Tattersall RB. Seven years experience of home management in pregnancy in women with insulin-dependent diabetes. *Diabet Med* 1984;1:199-204.

18. Standards of medical care in diabetes. *Diabetes Care* 2004;27 Suppl 1:S15-35.

19. Boland E, Monsod T, Delucia M, Brandt CA, Fernando S, Tamborlane WV. Limitations of conventional methods of self-monitoring of blood glucose: lessons learned from 3 days of continuous glucose sensing in pediatric patients with type 1 diabetes. *Diabetes Care* 2001;24:1858-1862.

20. Bolinder J, Hagstrom-Toft E, Ungerstedt U, Arner P. Self-monitoring of blood glucose in type I diabetic patients: comparison with continuous microdialysis measurements of glucose in subcutaneous adipose tissue during ordinary life conditions. *Diabetes Care* 1997;20:64-70.

21. Mastrototaro J. The MiniMed Continuous Glucose Monitoring System (CGMS). *J Pediatr Endocrinol Metab* 1999;12 Suppl 3:751-758.

22. Kerssen A, de Valk HW, Visser GHA. The Continuous Glucose Monitoring System during pregnancy of women with Type 1 diabetes mellitus; accuracy assesment. *Diabetes Technol Ther* 2004;6:645-651.

23. Diabetes mellitus. Report of a WHO Study Group. *World Health Organ Tech Rep Ser* 1985;727:1-113.

24. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;15:539-553.

25. Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, Taylor WF. Mean amplitude of glycemic excursions, a measure of diabetic instability. *Diabetes* 1970;19:644-655.

26. Evers IM, de Valk HW, Mol BW, ter Braak EW, Visser GH. Macrosomia despite good glycaemic control in Type I diabetic pregnancy; results of a nationwide study in The Netherlands. *Diabetologia* 2002;45:1484-1489.

27. Eriksson UJ, Cederberg J, Wentzel P. Congenital malformations in offspring of diabetic mothers--animal and human studies. *Rev Endocr Metab Disord* 2003;4:79-93.

28. Schwartz R, Teramo KA. Effects of diabetic pregnancy on the fetus and newborn. *Semin Perinatol* 2000;24:120-135.

29. Weintrob N, Karp M, Hod M. Short- and long-range complications in offspring of diabetic mothers. *J Diabetes Complications* 1996;10:294-301.

30. Berk MA, Mimouni F, Miodovnik M, Hertzberg V, Valuck J. Macrosomia in infants of insulin-dependent diabetic mothers. *Pediatrics* 1989;83:1029-1034.

31. Mountain KR. The infant of the diabetic mother. *Baillieres Clin Obstet Gynaecol* 1991;5:413-442.

32. Dalgic N, Ergenekon E, Soysal S, Koc E, Atalay Y, Gucuyener K. Transient neonatal hypoglycemia--long-term effects on neurodevelopmental outcome. *J Pediatr Endocrinol Metab* 2002;15:319-324.

33. Rosenn B, Siddiqi TA, Miodovnik M. Normalization of blood glucose in insulin-dependent diabetic pregnancies and the risks of hypoglycemia: a therapeutic dilemma. *Obstet Gynecol Surv* 1995;50:56-61.

34. Kimmerle R, Heinemann L, Delecki A, Berger M. Severe hypoglycemia incidence and predisposing factors in 85 pregnancies of type I diabetic women. *Diabetes Care* 1992;15:1034-1037.

35. Hellmuth E, Damm P, Molsted-Pedersen L, Bendtson I. Prevalence of nocturnal hypoglycemia in first trimester of pregnancy in patients with insulin treated diabetes mellitus. *Acta Obstet Gynecol Scand* 2000;79:958-962.

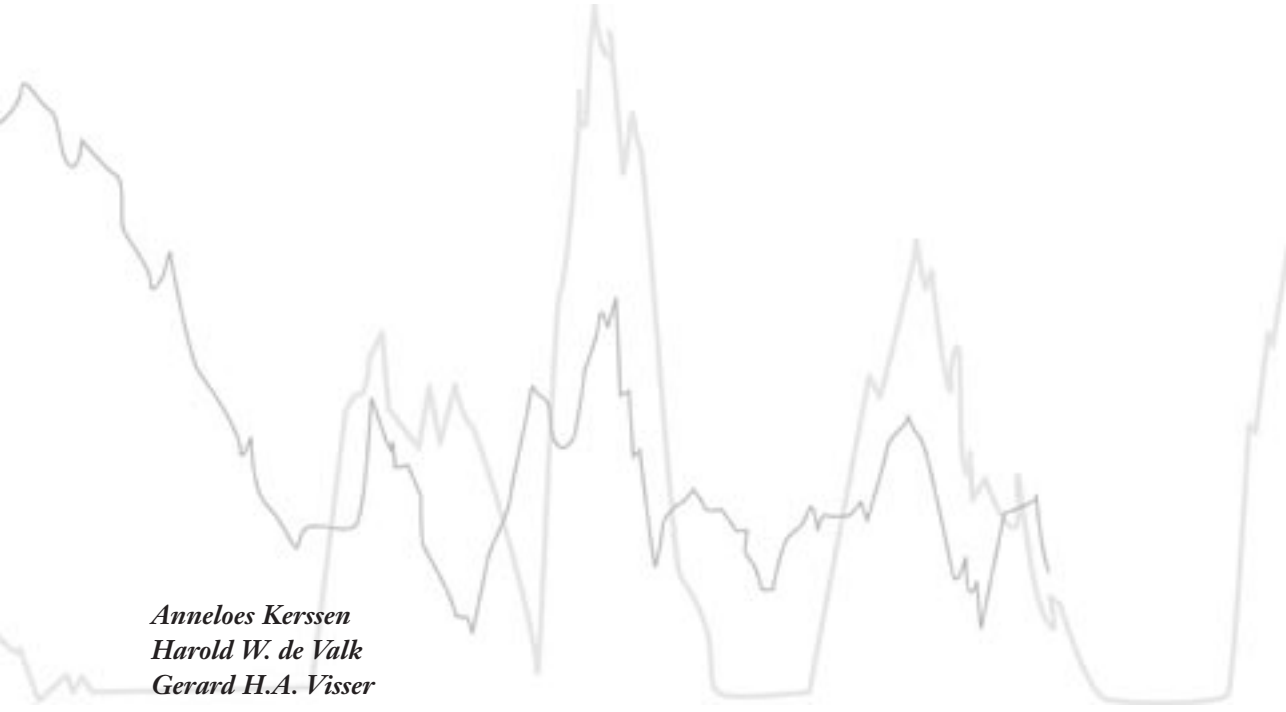
36. Evers IM, ter Braak EW, de Valk HW, van Der Schoot B, Janssen N, Visser GHA. Risk indicators predictive for severe hypoglycemia during the first trimester of type 1 diabetic pregnancy. *Diabetes Care* 2002;25:554-559.

37. Rayburn W, Piehl E, Jacober S, Schork A, Ploughman L. Severe hypoglycemia during pregnancy: its frequency and predisposing factors in diabetic women. *Int J Gynaecol Obstet* 1986;24:263-268.

7

Day-to-day glucose variability during pregnancy in women with type 1 diabetes mellitus:

glucose profiles measured with the Continuous Glucose Monitoring System



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Abstract

Objective To observe day-to-day variability in glucose levels in pregnant women with type 1 diabetes using the continuous glucose monitoring system (CGMS) and to assess the usefulness of continuous glucose measurements for adjustment of insulin treatment.

Methods Thirty-one pregnant women with type 1 diabetes used the CGMS for two consecutive days. Patients were classified in two groups (high versus low day-to-day variability) based on visual inspection of the glucose excursions. Mean absolute difference (MAD) was calculated for each patient as measure of day-to-day variability. The relationship between MAD and the variables HbA_{1c}, maternal age and BMI, duration of diabetes, number of self-monitored blood glucose levels, number of insulin injections, gestational age, nutrition, physical activity, White-classification, living with children and method of insulin administration was determined. The two days of the first twenty CGMS measurements were separated and four physicians were asked to give recommendations on treatment adjustment for each separate day.

Results Seventeen patients (55%) were classified as having low (MAD 0.92-2.33 mmol/l) and 14 (45%) as having high day-to-day variability (MAD 2.41-6.12 mmol/l). Of the variables measured, only the relation between MAD and HbA_{1c} was significant (r=0.58, p=0.001). The difference in recommendation on treatment adjustment between the days of the CGMS measurement ranged from 29-48%. This percentage was significantly higher in the high day-to-day variability group (48 vs. 33%, p=0.01).

Conclusion Day-to-day glucose variability is high and a problem in the treatment of pregnant women with type 1 diabetes. Fine-tuning of insulin regimens based on two-day measurements with the CGMS is not advisable.

Introduction

In pregnant women with type 1 diabetes mellitus, glycaemic control is generally considered tight enough when the HbA_{1c}-level is below 7.0% (1% above the upper limit of normal range which is 4.0-6.0 %).[1] However, using the MiniMed Continuous Glucose Monitoring System (CGMS, MiniMed, Sylmar, CA 91342, USA), we have recently shown that there is a considerable within-day glucose variability in pregnant women with HbA_{1c}-levels in the 'safe' range (between 6.0 and 7.0%).[2] These women have transient, often unnoticed, periods of hyperglycaemia, which may explain the high incidence of fetal macrosomia and congenital malformations still observed in pregnancies of diabetic women with 'safe' HbA_{1c}-values.[2-4] The CGMS is a system that continuously measures glucose levels in the subcutaneous interstitial fluid of the abdomen and that works up to 72 hours. Several studies have shown that interstitial fluid glucose levels generally follow venous blood glucose levels and fingerstick measured capillary glucose levels.[5-8] The current intention for use of the CGMS is occasional and additional to standard invasive glucose measurement. Yogev *et al.*[9] published a paper suggesting that during pregnancy intermittent application of the CGMS can be used to fine-tune insulin regimens. However, such an adjustment seems only feasible if day-to-day variability is limited and could even be harmful when day-to-day variability is large. Potential reasons for day-to-day variability include variation in daily activities such as changes in diet, exercise and emotional state.[10]
It was the objective of this study to observe the extent of day-to-day variability in glucose levels in pregnant women with type 1 diabetes mellitus using the CGMS and to look for possible factors associated with day-to-day glucose variation. Furthermore, this study was aimed at assessing the usefulness of continuous glucose measurements with the CGMS for adjustment of insulin treatment during pregnancy.

Materials and methods

Patients

Thirty-one pregnant women with type 1 diabetes mellitus were recruited from the obstetric outpatient clinic of the University Medical Center Utrecht, The Netherlands. Only women with singleton pregnancies were asked to participate. The Ethical Committee of the University Medical Center Utrecht, The Netherlands, approved the study. Participants gave written informed consent.

The Continuous Glucose Monitoring System

Patients were asked to wear a Continuous Glucose Monitoring System (CGMS) for three successive regular weekdays. The CGMS measures glucose levels in the

extracellular fluid of the abdominal subcutaneous tissue every ten seconds through electrochemical reaction of the glucose with glucose oxidase. The CGMS stores values within a range of 2.2-22.2 mmol/l (40-400mg/dl) every five minutes providing 288 readings in 24 hours. 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 enter data from at least four fingerstick glucose measurements each day for calibration of the system.
The data from the CGMS are considered valid if three criteria for optimal accuracy are met: 1) at least four paired sensor glucose / meter glucose readings per day. 2) correlation coefficient between sensor glucose values and meter blood glucose readings ≥ 0.79. 3) average value of differences between sensor glucose values and meter glucose values for a given day $\leq 28\%$.[11]
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 48 hours of each measurement that fit these criteria were used for analyses.

Day-to-day and within-day variability

Moberg *et al.*[12] described the mean absolute difference (MAD) as estimation of the difference in glucose excursions between consecutive days. The MAD is calculated by adding the absolute differences of all blood glucose values and dividing them by the number of values minus one.[12] Of each patient MAD was calculated as measure for day-to-day variability.
However, no criteria for the classification of day-to-day variability into high or low have been described. We therefore classified patients into high and low day-to-day variability based on visual inspection of the continuous glucose measurements and related this classification to the actual MAD values. Six physicians were given a print-out with the two days of the continuous glucose measurement of each patient projected over each other and were asked to classify them in one of two groups on basis of visual inspection: a group whose glucose excursion of day 1 resembles that of day 2 (Group I), and a group whose glucose excursion of day 1 did not resemble the glucose excursion of day 2 (Group II). The physicians were unaware of the identity and MAD of the patient, HbA_{1c}-level, type and dose of insulin treatment and the duration of pregnancy.
Within-day glucose variability was expressed as coefficient of variance (CV=100 x SD/mean). The CV of each measurement day of each patient was calculated. CV is expressed as mean over the two days (CV_{mean}) and as difference between day 1 and day 2 ($CV_{difference}$). The relationship between MAD and CV_{mean} and $CV_{difference}$ was analysed using the Pearson correlation coefficient.

Variables

Information on variables possibly associated with day-to-day glucose variatiability was obtained either from the patients' medical record or from a diary each patient kept of the days the CGMS was used.

HbA_{1c} -level.

HbA_{1c}-levels were measured within one week after the continuous glucose measurement. Normal range is 4.0 to 6.0%.

Maternal age.

Age in years on the first day of the continuous glucose measurement.

Duration of diabetes.

Number of years since onset of the diabetes on the first day of the continuous glucose measurement.

Prepregnancy maternal body mass index (BMI).

BMI (kg/m^2) calculated from the patients height and weight measured before pregnancy.

Gestational age.

Gestational age in weeks on the first day of the continuous glucose measurement. Gestational age was either determined by sonographic measurement of the crown-rump-length (CRL) or calculation from the first day of the last menstruation (in women with a regular menstrual cycle).

White- classification.

Diabetes was classified according to the White-classification, which is based on age of onset of diabetes, duration of diabetes and the presence of complications such as nephropathy and retinopathy.[13] This classification includes the following categories:

- White B, onset of diabetes ≥20 years of age or duration of diabetes ≤10 years;
- White C, onset of diabetes at 10-19 years of age or duration of diabetes 10-19 years;
- White D, onset of diabetes <10 years of age or duration of diabetes ≥20 years and/or presence of benign retinopathy;
- White F, presence of nephropathy;
- White R presence of proliferative retinopathy.

Living with children.

Being a parent influences life-style and therefore patients were categorised as having or not having children living with them.

Method of insulin administration.

Expressed as Continuous Subcutaneous Insulin Injections (CSII) or multiple injection schedule (MIS).

Self-monitored blood glucose measurements.

Number of fingerstick blood glucose measurements per day expressed as mean over the two days (BG_{mean}) and as difference between day 1 and day 2 ($BG_{difference}$).

Insulin injections.
Number of insulin injections (MIS) or extra insulin boluses (CSII) per day expressed as mean over the two days (Ins_{mean}) and as difference between day 1 and day 2 ($Ins_{difference}$).
Type of day.
All measurements were made on weekdays. As daily routine and amount of stress are often different on a day at work versus a non-working day and most patients work part-time, the following classification was made: both days at work/ both not at work versus one day at work and one day not at work.
Physical activity.
Number of hours the patient had physical activity on the days of the continuous glucose measurement.
Nutrition.
Difference between number of calories ingested on day 1 and number of calories ingested on day 2.

Statistics

The relationship between MAD and continuous distributed variables was analysed using the Pearson correlation coefficient. Difference in mean MAD between the groups of nominal distributed variables was analysed using the independent samples T-test. Difference in mean MAD between the different categories of the White classification was analysed using the Kruskal-Wallis H test. P-values <0.05 were considered significant.

Treatment

The 48-hour continuous glucose measurements of the first twenty patients were split into two separate days giving forty 24-hour glucose profiles. Four physicians were asked to indicate whether they would lower, elevate or continue the level of used insulin during fixed time intervals in each of the forty glucose profiles. The physicians were unaware of which two glucose profiles originated from the same patient and of the identity of the patients. Depending on method of insulin administration (CSII or MIS) there were two schedules with fixed periods of time to which the treatment recommendation related: 1) CSII: 0.00-04.00 h, 04.00-06.00 h, 06.00-12.00 h, 12.00-18.00 h and 18.00-24.00 h and extra boluses before meals (breakfast, lunch, dinner); 2) MIS: Basal insulin and meal-time insulin (before breakfast, lunch and dinner). This gave eight treatment recommendations per day when CSII was used and four treatment recommendations per day when MIS was used.
Treatment recommendation was classified as follows: a decrease in insulin level (-1), unchanged insulin level (0), an increase in insulin level (1). For each patient and each physician, the number of differences in treatment recommendation between day 1 and day 2 was calculated and expressed as percentage of total number of

treatment recommendations. Analysis was performed on the total group and groups I (low day-to-day variability) and II (high day-to-day variability) separately. Percentage of difference in treatment recommendation for each patient was correlated with MAD of that patient using the Pearson correlation coefficient. Percentage of difference in treatment recommendation for all patients combined was compared between group I and group II using the Chi-square test.

Results

Characterising patients

All thirty-one pregnant women with type 1 diabetes mellitus who were asked for this study participated. There were no adverse events associated with the use of the CGMS. Each patient had a continuous glucose measurement of at least 48 hours fit for analysis (no missing measurements, accuracy criteria met). Median age of the patients was 34 years (range 28 to 44 years), median duration of diabetes was 18 years (range 1 to 28 years), median HbA_{1c} was 6.4% (range 5.3 to 8.2%, 4 patients had HbA_{1c} > 7.0%) and median maternal pre-pregnancy BMI was 26.0 kg/m^2 (range 20.4 to 42.9 kg/m^2). There were 16 nullipara, 11 women were para 1, three women were para 2 and one woman was para 3. Twenty-two patients were in the first trimester of pregnancy (gestational age ranging from 9 to 14 weeks), five in the second trimester of pregnancy (gestational age ranging from 25 to 28 weeks) and four in the last trimester of pregnancy (gestational age ranging from 32 to 38 weeks). Eight patients were classified as White B, ten as White C, five as White D, four as White F, three as White R and one as White FR. Seventeen patients were treated with CSII while the remaining fourteen patients were treated with MIS. All patients practised self-monitoring of blood glucose levels.

Day-to-day and within-day variability

MAD ranged from 0.92 to 6.12 mmol/l with a median of 2.30 mmol/l. Seventeen patients (55%) were classified as having low day-to-day glucose variation (Group I). Fourteen patients (45%) were classified as having high day-to-day glucose variation (Group II). MAD in Group I ranged from 0.92 to 2.33 mmol/l and MAD in Group II ranged from 2.41 to 6.12 mmol/l, i.e. there was no overlap between both groups (*Figure 1*). *Figure 2* shows glucose profiles of two patients with a MAD <2.35 mmol/l. *Figure 3* shows glucose profiles of two patients with a MAD >2.35 mmol/l. CV_{mean} ranged from 14.4 to 68.2% with a median of 34.3%. $CV_{difference}$ ranged from 0.13 to 39.3% with a median of 9.2%. Correlation coefficient for the relation between MAD and CV_{mean} was 0.76 ($p<0.001$). Correlation coefficient for the relation between MAD and $CV_{difference}$ was 0.47 ($p<0.001$).

Table 1. Correlation coefficients, means and significance levels of relationship between MAD and variables.

		Correlation coefficient (*r*)	Significance (p)
HbA_{1c}		0.58	0.001*
Maternal age		-0.22	0.22
Duration of diabetes		0.28	0.13
Prepregnancy BMI		0.03	0.89
Gestational age		-0.27	0.15
BGmean		-0.24	0.20
BGdifference		-0.30	0.87
Insmean		-0.13	0.51
Insdifference		0.09	0.64
Nutrition		0.02	0.95
		Mean MAD	Significance (p)
White classification	B	10.6**	0.29
	C	17.7**	
	D	17.6**	
	F	14.3**	
	R	24.7**	
	FR	15.0**	
Living with children	Yes	3.05	0.25
	No	2.44	
Method of insulin administration	CSII	2.49	0.59
	MIS	3.03	
Activity level †	Similar	2.73	0.99
	Different	2.74	

* significant < 0.01

** mean rank of MAD

† Patients with both days at work /not at work and patients with physical activity on both days or neither of these days were classified as 'similar'. Patients with one day at work and one day not at work or physical activity on only one of the two measurement days are classified as 'different'.

Comparison of variables

Table 1 shows correlation coefficients, means and significance level of the relationship between MAD and the variables. Only the relation between MAD and HbA_{1c} was significant (r=0.58, p<0.001).

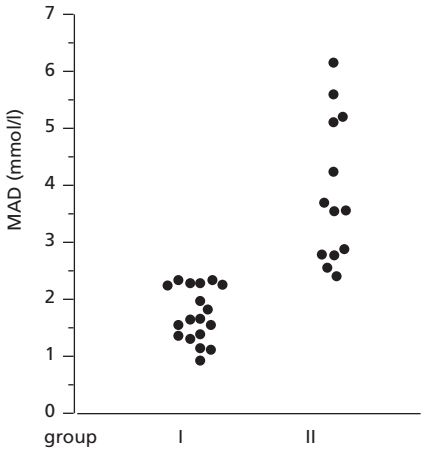

Figure 1. MAD and group number. Group I: Patients with low day-to-day variability based on visual classification. Group II: Patients with high day-to-day variability based on visual classification.

Three patients had physical exercise on one of the two measurement days, the remaining patients did not exercise during the days of continuous glucose monitoring. Three patients had a working day as day 1 and a non-working day as day 2; the remaining patients had two identical measurement days (either working or non-working). These six patients with different activity level on day 1 versus day 2 were joined as one group. Comparison of mean MAD of this group with that of the 25 patients with similar activity levels on day 1 versus day 2 shows no significant difference (*Table 1*)

Treatment

Table 2 shows percentage of difference in treatment recommendation between day 1 and day 2 of the continuous glucose measurement given by each physician. Correlation coefficient between MAD and percentage of difference in treatment recommendation given for each patient was 0.57 ($p<0.01$). Percentage of difference in treatment recommendation was significantly lower in group I compared to group II (33 vs. 48%, $p<0.01$)

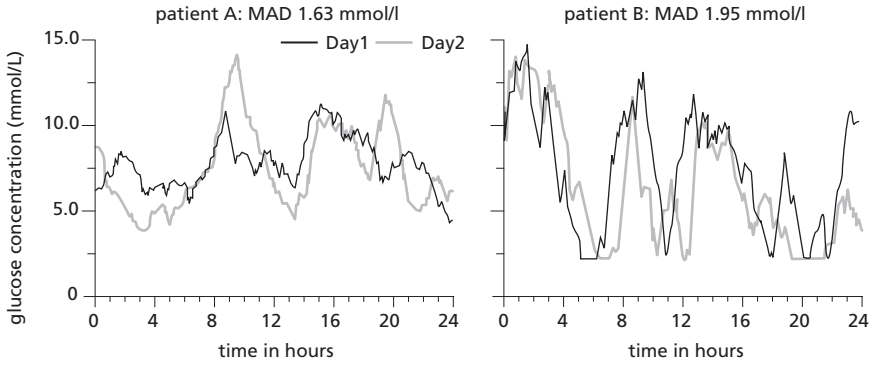

Figure 2. Two-day continuous glucose monitoring profiles of two women with MAD <2.35 mmol/l.

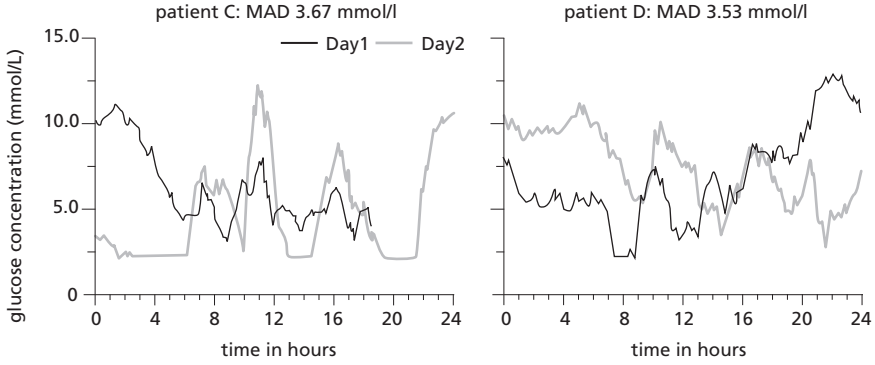

Figure 3. Two-day continuous glucose monitoring profiles of two women with MAD >2.35 mmol/l.

Table 2. Percentage of difference in treatment recommendation given by each physician between day 1 and day 2 of the continuous glucose measurement.

Physician	Difference in recommendation Both groups	Difference in recommendation Group I*	Difference in recommendation Group II**
1	29%	22%	38%
2	38%	36%	40%
3	43%	33%	55%
4	48%	40%	58%
Total	39%	33%	48%

* low day-to-day variability

** high day-to-day variability

Discussion

This study confirms the findings of earlier studies that continuous glucose monitoring during pregnancy reveals a relatively large within-day variation in glucose levels that may otherwise remain unnoticed.[2,9] These, otherwise unnoticed, episodes of hyper- and hypoglycaemia may be the reason for the persisting increased incidence of congenital malformations and fetal macrosomia in women with type 1 diabetes mellitus. Detailed information on glucose excursions may be helpful in adjusting insulin treatment,[9] but that requires a sufficient day-to-day stability of glucose values. Determination of the degree of day-to-day variability is hampered by the lack of accepted criteria.

We used a visual inspection of the continuous glucose measurements to classify the day-to-day fluctuations into high or low by asking 6 physicians to come to an agreement as to the traces of all 31 women. Such an agreement was easily reached and examples of the two categories are shown. Post hoc analysis of the MAD between both days revealed that there was a cut-off point with a MAD of about 2.35 mmol/l between patients with a low and high day-to-day variation as judged visually, without overlap between the groups. Since pattern recognition is usually easier done by eye than by numerical analysis, and since this procedure resulted in a clear cut-off MAD value between both groups, this value may be used in future studies on day-to-day variation. For the analysis of the variables, however, we chose to use the MAD as a continuous variable in studying the relationships with possible factors influencing day-to-day variability.

Almost half of our patients showed a large day-to-day variation. This seriously hampers insulin adjustment on the basis of the information of the CGMS. This is the more so since most patient characteristics did not discriminate between those with a low or high glucose variation. Women with a low day-to-day variation had a lower within-day variation and a lower HbA_{1c}-level. High within-day variation often means alternation between post-prandial hyperglycaemia's and pre-meal hypoglycaemia's. Initially we hypothesised that the chance of these fluctuations occurring at the exact same time on two consecutive days is small due to variations in rhythm of meals, exercise, sleep, etc. However, the finding that mean MAD in the group of women with different daily activities is almost identical to the mean MAD of women with similar daily activities on the measurement days does not confirm this. It is the question whether parameters such as 'work day or not' and 'hours of physical activity' are reliable representatives of activity level. In some cases, for example in families with small children, it is plausible that a day at work may be less emotional and stressful than a day at home. Reservation in forming conclusions based on these latest findings is therefore appropriate and a more reliable parameter for daily activity and stress should be used in future research.

Analysis of treatment strategy shows that in 29-48% of the cases physicians gave different recommendations on the two separate days. The percentage of difference

in treatment recommendation was positively related to degree of day-to-day variability and significantly higher in patients with high day-to-day variability. This means that daily continuous glucose profiles are of lowest value in patients in whom it should be of highest importance as insulin treatment adjustment is most difficult in patients with high MAD (and high HbA_{1c}). Fine-tuning of insulin regimen through intermittent application of the CGMS as suggested by Yogev *et al.*[9], should therefore, if at all, be done with the utmost caution. The CGMS measurement can, however, be useful in increasing the patients' awareness of variations in glucose levels. The glucose profiles may be of help in the adjustment of eating habits and regularity of living pattern. This might lead to less day-to-day variability in a second CGMS measurement making fine-tuning of insulin regimens easier and more reliable. We agree with Yogev *et al.*[9] that the CGMS provides more information than 6-8 fingerstick measurements a day, which makes it helpful in the treatment of diabetes in pregnant women. However, their study does not take day-to-day variability into account and no comparison between insulin adjustment recommendations for separate days of the same CGMS measurement was made. Therefore, the difficulties internists have in fine-tuning insulin regimens in pregnant women with diabetes as shown in the present study, do not become apparent in their study.

As insulin adjustment on the basis of the information of two days of continuous glucose monitoring is hampered by day-to-day variation, the question arises whether this will change when patients are monitored for more than two days. The pathofysiologic mechanism responsible for fluctuations in glucose profiles seems to be more complex than the individual variables analysed in this study. Further research will have to show whether day-to-day variability will increase or decrease with more than two measurement days.

In conclusion, day-to-day variability in glucose profiles is an important problem in the treatment of pregnant women with type 1 diabetes mellitus. Further research will be aimed at the determination of explanatory factors such as stress, diabetic autonomic neuropathy (gastric motility) and eating patterns. It is also important to find out whether day-to-day variability will remain low in patients with a low day-to-day variability over two days when they are monitored for more days. If so, than in that group - i.e. in half of the patients - continuous glucose measurements may be useful for the adjustment of insulin treatment. Continuous glucose measurements in patients with high day-to-day variability may be useful in increasing the patients' awareness of variations in glucose levels and may be useful in exploring specific reasons for and patterns of high day-to-day variability.

References

1. ADA. Preconception care of women with diabetes. *Diabetes Care* 2003;26 Suppl 1:S91-S93.
2. Kerssen A, Evers IM, Valk de 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* 2003;13:309-313.
3. Evers IM, de Valk HW, Mol BW, ter Braak EW, Visser GH. Macrosomia despite good glycaemic control in Type I diabetic pregnancy; results of a nationwide study in The Netherlands. *Diabetologia* 2002;45:1484-1489.
4. 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* 2004;328:915.
5. Bantle JP, Thomas W. Glucose measurement in patients with diabetes mellitus with dermal interstitial fluid. *J Lab Clin Med* 1997;130:436-441.
6. Fischer U. Continuous in vivo monitoring in diabetes: the subcutaneous glucose concentration. *Acta Anaesthesiol Scand Suppl* 1995;104:21-29.
7. Sternberg F, Meyerhoff C, Mennel FJ, Bischof F, Pfeiffer EF. Subcutaneous glucose concentration in humans. Real estimation and continuous monitoring. *Diabetes Care* 1995;18:1266-1269.
8. Sternberg F, Meyerhoff C, Mennel FJ, Mayer H, Bischof F, Pfeiffer EF. Does fall in tissue glucose precede fall in blood glucose? *Diabetologia* 1996;39:609-612.
9. Yogev Y, Chen R, Ben-Haroush A, Phillip M, Jovanovic L, Hod M. Continuous glucose monitoring for the evaluation of gravid women with type 1 diabetes mellitus. *Obstet Gynecol* 2003;101:633-638.
10. Zehrer C, Hansen R, Bantle J. Reducing blood glucose variability by use of abdominal insulin injection sites. *Diabetes Educ* 1990;16:474-477.
11. Mastrototaro J. The MiniMed Continuous Glucose Monitoring System (CGMS). *J Pediatr Endocrinol Metab* 1999;12 Suppl 3:751-758.
12. Moberg E, Kollind M, Lins PE, Adamson U. Estimation of blood-glucose variability in patients with insulin-dependent diabetes mellitus. *Scand J Clin Lab Invest* 1993;53:507-514.
13. White P. Diabetes mellitus in pregnancy. *Clin Perinatol* 1974;1:1331-1347.

8

Two- or three-day continuous glucose measurements in pregnant women with type 1 diabetes mellitus?

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Abstract

To safely adjust insulin regimens on basis of measurements with the Continuous Glucose Monitoring System (CGMS) in pregnant women with type 1 diabetes, low day-to-day variability is necessary. Evaluation of 36 three-day continuous glucose measurements of these women shows that in 88% of the patients with low day-to-day variability, glucose profile of the third measurement day did not differ from that of the previous measurement days. Two days of continuous glucose measurement therefore seems to be enough for the identification of patients with low day-to-day variability and the adjustment of insulin regimens in these patients.

Introduction

Treatment of diabetes in pregnant women with type 1 diabetes mellitus is essential for both mother and infant as these pregnancies are often accompanied by complications such as severe maternal hypoglycaemia, congenital fetal malformations, sudden infant death and macrosomia.[1] Goal of the treatment is to achieve a pregnancy outcome that is equal to that of women without diabetes mellitus. The Continuous Glucose Monitoring System (CGMS) is a useful additional tool to achieve optimal glycemic control.[2,3] In an earlier paper we have shown that low day-to-day variability in glucose levels of pregnant women with type 1 diabetes mellitus is essential for adequate treatment.[4] Evaluation of 48-hour glucose profiles measured with the Continuous Glucose Monitoring System (CGMS) in 31 pregnant women with type 1 diabetes, has shown that low day-to-day variability is achieved in almost half of the pregnant women with type 1 diabetes and that only in these patients fine-tuning of insulin regimens based on the CGMS profiles seems to be safe. In patients with high day-to-day variability the CGMS is of help in increasing the patients' awareness of variations in glucose levels and in the adjustment of eating habits and regularity of living pattern. In that study two-day measurements were used and the question arose whether day-to-day variability is constant or changes when patients are monitored for more days. In other words, is it useful to measure patients for three days or will two days suffice?

Methods

In order to answer this question, three-day CGMS measurements of 36 pregnant women with type 1 diabetes mellitus were analysed. These measurements were selected from a data base of 100 CGMS measurements in 47 pregnant women with type 1 diabetes and included all women in whom continuous glucose measurements met the manufacturers accuracy criteria during the whole study period and in whom the measurement lasted at least three successive uninterrupted calendar days.[5] The 64 unused measurements did not consist of three successive uninterrupted technically accurate calendar days. This is mainly due to the fact that at initiation of the CGMS measurements in our clinic in December 2001 the quality of the CGMS was less than it currently is, often cutting the measurement interval short. At this moment, CGMS measurements with a measurement interval of 72 hours or more are regularly obtained.

The Mean Absolute Difference (MAD) of the glucose profiles was used as measure of day-to-day variability.[6] The MAD is calculated by adding the absolute differences of all blood glucose values and dividing them by the number of values minus one. The MAD of the glucose profiles of the first two days of each measurement (MAD_1) was compared with the MAD of the glucose profiles of the second and

third day of the CGMS measurement (MAD_2). Earlier we found that patients can be classified into low or high day-to-day variability based on the MAD and that the MAD value that discriminates between these groups is 2.35 mmol/l.[4] Each patient was classified into high or low day-to-day variability based on MAD_1 and MAD_2. Difference in classification based on MAD_1 and MAD_2 and Pearson correlation coefficient between MAD_1 and MAD_2 were used as outcome measure. HbA_{1c} and gestational age were compared between the patients with stable MAD and patients with difference in classification using the Mann-Whitney U test with p=0.05 as significance level.

Results

Gestational age of the 36 pregnant women ranged from 9 2/7 to 37 6/7 weeks. HbA_{1c} ranged from 5.1 to 8.2% with a median of 6.6% (normal range 4.0-6.0%). MAD_1 correlated significantly with MAD_2 (r=0.84, p< 0.001). Based on MAD_1 47% (n=17) of the patients were classified as having low day-to-day variability and 53% (n=19) were classified as having high day-to-day variability. Six patients (17%) changed groups when the classification was based on MAD_2 instead of MAD_1;

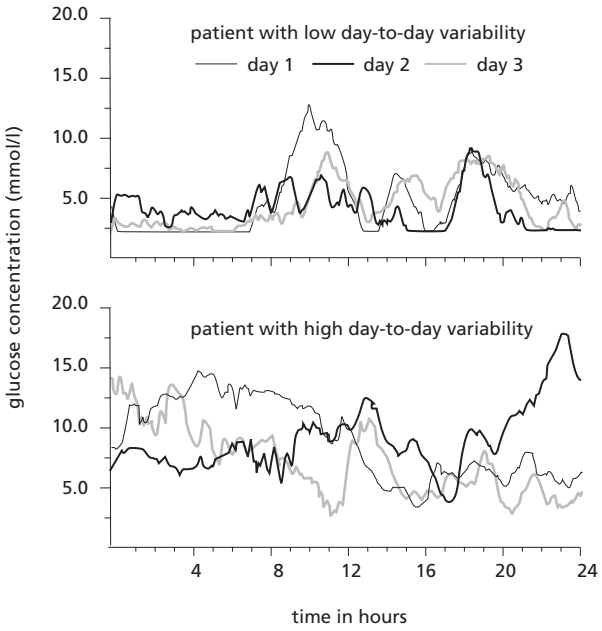

Figure 1. Example of patient with low (MAD_1=1.58 and MAD_2=1.66 mmol/l) and high (MAD_1=3.99 and MAD_2=4.24 mmol/l) day-to-day variability.

two (6%) were classified as high instead of low day-to-day variability and four (11%) were classified as low instead of high day-to-day variability. *Figure 1* shows examples of a patient with low and a patient with high day-to-day variability in three measurement days.
There was no difference in HbA_{1c} and gestational age between the patients with stable MAD and patients that changed groups (p=0.92 and p=0.44, respectively).

Discussion

Stable day-to-day glucose levels are essential for the treatment of pregnant women with type 1 diabetes mellitus. Low day-to-day glucose variability is found in about half of the patients when they are measured for two days.[4] Adjustment of insulin regimens based on CGMS profiles seems possible in these patients provided that two days of continuous monitoring is sufficient to study day-to-day variability. In the present study we found that in the group of patients with low day-to-day variability MAD did not change in 88% (15 out of 17) of the cases when patients were measured for three days. In these patients the third day of the CGMS measurement is, therefore, not of much additional use for the adjustment of insulin regimens and 2 days of measurement is enough.
Women with a high day-to-day variability between day one and day two usually (in 79% or 15 out of 19 of the cases) had a high variability between day two and three. In these patients adjustment of insulin regimens on the basis of CGMS measurements does not seem to be possible.[4] This study shows that two days of CGMS measurement is enough to identify the women with high day-to-day variability. However, CGMS measurements also give information that is useful for the adaptation of eating- or living habits of the patient. Thus, CGMS measurements are useful in patients with high day-to-day variability. It remains to be seen if a third day of measurement is necessary to increase the awareness of variations in glucose levels leading to the adjustment of eating habits and regularity of living pattern.
In conclusion, if CGMS measurements are used for the adjustment of insulin regimens in pregnant women with type 1 diabetes, two days of measurement seems to be enough. Low day-to-day variability is needed for the safe and adequate adjustment of insulin regimens and two days of CGMS measurement is generally enough to discriminate between women with low and women with high day-to-day variability. We therefore propose that, in pregnant women with type 1 diabetes, the CGMS measurement period is shortened to two days. This is the more if one imagines the inconvenience of being pregnant and having the CGMS on one and an insulin pump on the other side of the belly.

References

1. Evers IM, de Valk HW, Visser GHA. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. *BMJ* 2004;328:915.
2. Bode BW, Gross TM, Thornton KR, Mastrototaro JJ. Continuous glucose monitoring used to adjust diabetes therapy improves glycosylated hemoglobin: a pilot study. *Diabetes Res Clin Pract* 1999;46:183-190.
3. Yogev Y, Chen R, Ben-Haroush A, Phillip M, Jovanovic L, Hod M. Continuous glucose monitoring for the evaluation of gravid women with type 1 diabetes mellitus. *Obstet Gynecol* 2003;101:633-638.
4. Kerssen A, de Valk HW, Visser GHA. Day-to-day glucose variability during pregnancy in women with Type 1 diabetes mellitus: glucose profiles measured with the Continuous Glucose Monitoring System. *BJOG* 2004;111:919-924.
5. Mastrototaro J. The MiniMed Continuous Glucose Monitoring System (CGMS). *J Pediatr Endocrinol Metab* 1999;12 Suppl 3:751-758.
6. Moberg E, Kollind M, Lins PE, Adamson U. Estimation of blood-glucose variability in patients with insulin-dependent diabetes mellitus. *Scand J Clin Lab Invest* 1993;53:507-514.

9

Sibling birth weight as predictor of macrosomia in women with type 1 diabetes mellitus

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Abstract

Objective To establish the value of HbA_{1c}-levels and older sibling birth weight as predictors of birth weight and macrosomia in the offspring of women with type 1 diabetes mellitus.

Methods A total of 214 pregnancies of 107 women with type 1 diabetes were studied. Regression analysis was performed to test the predictive value of birth weight of first-born infant, HbA_{1c}-level, maternal BMI, maternal age and time between subsequent births on birth weight of the second-born infant. Birth weights were corrected for gender and gestational age. Percentages of macrosomic infants (weight >90^{th} centile) were calculated and compared between first- and second-born infants.

Results Only birth weight of earlier born infants was significantly related to that of second-born infants ($p<0.001$) and 40-50% of the variation in birth weight of second-born infants could be explained by birth weight of the first-born infants. About 85% of the mothers who gave birth to a macrosomic infant, had a macrosomic infant at a subsequent pregnancy.

Conclusion Although it is clear that glycaemic control contributes to birth weight in women with type 1 diabetes, birth weight of an earlier born infant appears to be a much better predictor for birth weight of a subsequent infant than HbA_{1c}-level during pregnancy. It may, therefore, be used for the identification of patients at risk of giving birth to a macrosomic infant. Day-to-day home monitoring of glucose levels rather than HbA_{1c}-levels should be used for the assessment of maternal glycaemia during pregnancy.

Introduction

Macrosomia is a frequent complication in pregnancies of women with type 1 diabetes mellitus.[1-4] Macrosomia may lead to short term complications such as increased rates of caesarean section, shoulder dystocia and neonatal hypoglycaemia. [5-10] Long term complications include increased risks for obesity, diabetes and breast carcinoma later in life.[11,12] It is generally agreed that macrosomia rate decreases when diabetic control in pregnant women with type 1 diabetes is tightened.[13,14] However, even in patients with near-normal HbA_{1c}-levels, macrosomia rates remains high.[2,4,5] Several studies on the relationship between HbA_{1c}-levels and birth weight have been published.[15-19] It has proved difficult to establish a clear relationship between HbA_{1c}-levels and infant birth weight. Positive[18,20] and negative[19,21] correlations between first trimester HbA_{1c}-level and infant birth weight have both been reported while other studies have shown that third trimester HbA_{1c}-levels are positively related to infant birth weight.[1,2] Similarity in these studies is that the relation between HbA_{1c}-levels and infant birth weight is weak. HbA_{1c}-levels account for less than 10% of the variance found in birth weight of infants of mothers with type 1 diabetes[2,19]. This raises questions concerning the usefulness of HbA_{1c}-levels as predictor of fetal macrosomia in pregnant women with type 1 diabetes mellitus.

In the non-diabetic population, birth weight of younger siblings has been shown to correlate with that of older siblings.[22,23] Reported correlations of sibling weight are strong and predictive values range from 20 to 30%.[22,23] In the general population, women with a macrosomic infant are ten times more likely to have a macrosomic infant at a subsequent birth than women with an appropriate for gestational age infant.[24] The relationship between sibling birth weights in women with type 1 diabetes has not been studied yet.

This study was aimed at establishing the value of HbA_{1c}-levels and older sibling birth weight as predictors of birth weight and macrosomia in the offspring of women with type 1 diabetes mellitus.

Materials and methods

Data of 266 pregnancies in 133 women with type 1 diabetes mellitus were obtained using the medical records of women who visited our clinic between January 1994 and June 2004 and the study records of women who participated in the nation-wide study 'Type 1 diabetes mellitus and pregnancy in the Netherlands anno 1999-2000' that was performed at our clinic.[3] The ethics committee of the University Medical Centre Utrecht had approved the latter study and all patients participating in that study gave written informed consent. Only women who gave birth to two live-born infants after 35 weeks of gestation were included in the present study.

Twenty-one women gave birth to an infant with a congenital malformation in one of the two pregnancies (7.9%). Five women gave birth to twins in one of the two pregnancies (1.9%). These 26 women (52 pregnancies) were excluded from the study. The remaining 107 women (214 pregnancies) were entered in the analysis. In 15 women at least one of the two pregnancies was complicated by a hypertensive disorder (pregnancy induced hypertension or pre-eclampsia). Hypertensive disorders of the mother are known to have a negative effect on birth weight of the infant.[25,26] However, the effect of hypertensive disorders on birth weight of the infant seems to be smaller or even absent when women deliver >37 weeks of gestation.[27,28] In the present study, analysis was therefore performed with and without exclusion of these 15 women.

As the study was performed retrospectively and no standards (number and moment) for the determination of HbA_{1c}-levels during pregnancy were used, HbA_{1c}-levels were calculated by computing the means of HbA_{1c}-levels determined in the first and the second half of the pregnancy. A standardization procedure was adopted to adjust for variations between HbA_{1c}-assays in different clinics.[3,29] Each local HbA_{1c}-value was first standardized using the mean (XN) and standard deviation (SDN) for a local non-diabetic population. These scores [$ZHbA_{1c}=(HbA_{1c}-XN)/SDN$] were then transformed back to percent units using the mean (5.0%) and standard deviation (0.5%) of the Utrecht assay as follows: $HbA_{1c}=0.5\%(ZHbA_{1c})+5.0\%$.

Birth weight was expressed as percentage of the Dutch population mean corrected for gender and gestational age and as weight centile[30]. Maternal Body Mass Index (BMI) before the second pregnancy, maternal age at birth of the second child and time that elapsed between the two births were computed from the data in the records.

Stepwise multiple linear regression analysis was used to evaluate the influence of birth weight of the older sibling, HbA_{1c}-level during the first and second half of the second pregnancy, maternal BMI, maternal age and the time elapsed between births on birth weight of the second-born child. This analysis was repeated after exclusion of the 15 women in whom hypertensive disorders complicated at least one of the two pregnancies.

Three subgroups were made based on the birth weight centiles of the first-born infants, corrected for sex and gestational age: (1) normal weight: weight centile <p90; (2) macrosomia: weight centile p90-p97.7; (3) severe macrosomia: weight centile ≥p97.7. Within each of these groups percentages of second-born infants with normal weight, macrosomia and severe macrosomia were calculated. Chi-square statistics were used to test whether there is a relation between birth weight groups of the first- and second-born sibling. Post hoc Cramer's V was used to describe the strength of the relationship. HbA_{1c}-levels of the women who had a normal weight infant and a severely macrosomic infant were compared between the two pregnancies using Wilcoxon statistics. For evaluation of statistical analyses, $p<0.05$ was considered significant.

Results

The regression analysis showed that birth weight of second-born infants was significantly related to birth weight of first-born infants and not to HbA_{1c}-level, maternal BMI, maternal age and time elapsed between births (*Table 1*). *Figure 1* shows the relation between birth weight of the first-born child and birth weight of the second-born child. *Figures 2a* and *2b* show the correlation between HbA_{1c}-levels in the first and second half of the pregnancy and birth weight of the infant. Exclusion of the 15 women with a hypertensive disorder in one or both of the pregnancies improved the correlation between birth weight of the first and the second child (r=0.737, r^2=0.544, p<0.001).
Of the first-born infants 44% had a birth weight within the normal range, 18% were macrosomic and 38% were severely macrosomic. Of the second-born infants 37% had a birth weight within the normal range, 16% were macrosomic and 47% were severely macrosomic. Percentages of concordance in birth weight groups are shown in *Table 2*. Chi-square and Cramer's V statistics showed that there is a significant and strong association between percentage of macrosomia in the first- and second-born infants of women with type 1 diabetes, V=0.507, p<0.001.
In 11 of the 12 women who had a normal weight and a severely macrosomic infant, the HbA_{1c}-levels during the first pregnancy could be retrieved from the medical records (*Table 3*). There was no significant difference in HbA_{1c}-levels during the first and second pregnancy in these women (p>0.8).

Table 1. Regression analysis of birth weight of first-born infant, HbA_{1c}-level during the first and second half of the second pregnancy, maternal BMI, maternal age and time elapsed between births by birth weight of second-born infant.

	R	R square	significance
- Birthweight of the first-born infant*	0.640	0.410	0.000
	Partial correlation		significance
- HbA_{1c}-level during the 1st half of the second pregnancy	0.173		0.192
- HbA_{1c}-level during the 2nd half of the second pregnancy	0.251		0.076
- Maternal BMI	0.116		0.453
- time elapsed between births	0.076		0.988
- maternal age	-0.042		1.000

* expressed as percentage of population mean corrected for gender and gestational age.

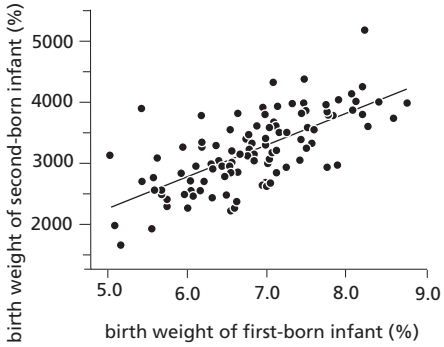

Figure 1. Correlation between birth weight of the first- and second-born infant (r=0.640, p<0.001)

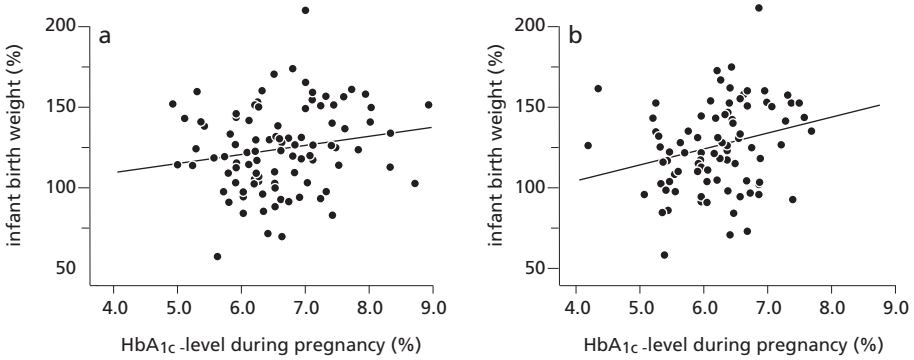

Figure 2. Correlation between (a) HbA_{1c}-level during first half of the second pregnancy and birth weight of second-born infant (r=0.173, NS) and (b) HbA_{1c}-level during the second half of the second pregnancy and birth weight of second-born infant (r=0.251, NS)

Table 2. Concordance in birthweight groups of siblings of mothers with type 1 diabetes mellitus.

	Second-born infant							
	normal birth weight		macrosomia		severe macrosomia		total	
	n	%	n	%	n	%	n	%
First-born infant								
normal birthweight	32	(68%)	5	(11%)	10	(21%)	47	(100%)
macrosomia (90-97.7 centile)	6	(32%)	8	(42%)	5	(26%)	19	(100%)
severe macrosomia (≥97.7 centile)	2	(5%)	17	(10%)	35	(85%)	41	(100%)

Table 3. HbA_{1c}-levels during pregnancy of women who gave birth to a normal weight and a severely macrosomic infant

Patient	First pregnancy	Second pregnancy
	Normal weight infant	Severely macrosomic infant
1	5.2	5.0
2	5.6	5.9
3	6.3	5.6
4	6.3	6.8
5	6.5	6.9
6	6.5	6.3
7	7.0	6.7
8	7.2	6.7
9	7.2	7.5
	Severely macrosomic infant	Normal weight infant
1	6.5	6.3
2	7.6	7.9

Discussion

Between 41 and 54% of the variation in birth-weight of second-born infants of mothers with type 1 diabetes mellitus could be explained by the birth weight of the first-born infant. HbA_{1c}-levels during pregnancy only explained between three and seven percent of the variations in birth weight and did not differ in two consecutive pregnancies of patients who gave birth to a normal weight and a severely macrosomic infant, respectively. We therefore conclude that birth weight of a previously born infant is a much stronger predictor for macrosomia than HbA_{1c} percentages. This is the more so since about 85% of the women who gave birth to a severely macrosomic infant in their first pregnancy, also had a severely macrosomic infant in their second pregnancy.

Macrosomia (birth weight >4000 g or >90th centile) is associated with higher rates of a prolonged first and second stage of labour, an increased risk of instrumental vaginal delivery, shoulder dystocia, cesarean birth, third and fourth-degree perineal lacerations, postpartum hemorrhage, prolonged hospital stay, Apgar score <4 and admission to the special care baby unit.[8,31,32] Prevention of macrosomia is therefore mandatory. The aetiology of macrosomia may be multifactorial, but there is evidence that (very) tight glycaemic control results in a lower incidence of macrosomic infants.[13,14,33] However, such a tight control is difficult to achieve and may cause maternal complications such as severe hypoglycaemia.[34] The present study helps to identify multiparae that may benefit most from a very tight glycaemic control.

In a non-diabetic population, gender of the infant, maternal age, parity and time since last pregnancy have been shown to explain about 20% of the variance in birth

weight.[22] Birth weight of the parents and maternal pre-pregnancy BMI have also been shown to correlate with birth weight of the offspring.[8,35-37] In the present study maternal BMI, maternal age and time elapsed since last pregnancy were not significantly related to birth weight of the second-born infant. This suggests that birth weight of offspring of women with diabetes is influenced in a different manner than that of offspring of a non-diabetic population. One may hypothesize that birth weight of infants of mothers with diabetes is indeed largely influenced by glucose levels (post-prandial hyperglycaemia). These glucose elevations, however, are of short duration and are therefore not reflected accurately by HbA_{1c}-levels, which are considered to be an expression of mean glucose values over a two- to three- month period.[38,39] Furthermore, since birth weight of an earlier born sibling is so strongly related, genetic or different diabetes-related intra-uterine factors cannot be ruled out.

Due to the retrospective nature of the study and the lack of guidelines for frequency and moment of determination of HbA_{1c}-levels during pregnancy, the number of data and gestational ages at determination of HbA_{1c}-level varied between patients. We attempted to overcome this heterogenity in the data set by using the mean HbA_{1c}-level during the first and second half of the pregnancy in the analysis. We acknowledge that analysis of HbA_{1c}-levels per trimester of the pregnancy as has been done in earlier studies would have been more accurate. However, since in our study differences in HbA_{1c}-levels accounted for approximately 5% of the observed variation in birth weight, a percentage similar to that found in previous studies,[2,19] our approach seems acceptable.

In conclusion, this study shows that HbA_{1c}-levels do not correlate with infant birth weight. It is clear that glycaemic control contributes to infant birth weight but that HbA_{1c}-level is not the correct measure for the determination of glycaemia during pregnancy when related to birth weight as the end-point. To assess the degree of glycaemic control that is achieved, daily self-monitoring of blood glucose levels should be used. A more reliable, although not perfect, predictor of infant birth weight is the birth weight of an earlier born infant. It can be used for the identification of patients at risk of giving birth to a macrosomic infant. Especially in these patients the achievement of tight glycaemic control during pregnancy is important.

References

1. Berk MA, Mimouni F, Miodovnik M, Hertzberg V, Valuck J. Macrosomia in infants of insulin-dependent diabetic mothers. *Pediatrics* 1989;83:1029-1034.
2. 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* 2002;45:1484-1489.
3. Evers IM, de Valk HW, Visser GHA. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. *BMJ* 2004;328:915.

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* 1997;315:279-281.
5. Cousins L. Pregnancy complications among diabetic women: review 1965-1985. *Obstet Gynecol Surv* 1987;42:140-149.
6. 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* 1991;165:831-837.
7. Schaefer-Graf UM, Rossi R, Buhrer C et al. Rate and risk factors of hypoglycemia in large-for-gestational-age newborn infants of nondiabetic mothers. *Am J Obstet Gynecol* 2002;187:913-917.
8. 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* 2003;111:9-14.
9. 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* 2003;188:1372-1378.
10. Meshari AA, De Silva S, Rahman I. Fetal macrosomia--maternal risks and fetal outcome. *Int J Gynaecol Obstet* 1990;32:215-222.
11. Van Assche FA, Holemans K, Aerts L. Fetal growth and consequences for later life. *J Perinat Med* 1998;26:337-346.
12. Samaras TT, Elrick H, Storms LH. Birthweight, rapid growth, cancer, and longevity: a review. *J Natl Med Assoc* 2003;95:1170-1183.
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* 1987;156:1089-1095.
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* 1996;13:170-174.
15. 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* 1996;103:427-433.
16. Lepercq J, Taupin P, Dubois-Laforgue D et al. Heterogeneity of fetal growth in type 1 diabetic pregnancy. *Diabetes Metab* 2001;27:339-344.
17. Combs CA, Gunderson E, Kitzmiller JL, Gavin LA, Main EK. Relationship of fetal macrosomia to maternal postprandial glucose control during pregnancy. *Diabetes Care* 1992;15:1251-1257.
18. Gold AE, Reilly R, Little J, Walker JD. The effect of glycemic control in the pre-conception period and early pregnancy on birth weight in women with IDDM. *Diabetes Care* 1998;21:535-538.
19. Johnstone FD, Mao JH, Steel JM, Prescott RJ, Hume R. Factors affecting fetal weight distribution in women with type I diabetes. *BJOG* 2000;107:1001-1006.
20. Rey E, Attie C, Bonin A. The effects of first-trimester diabetes control on the incidence of macrosomia. *Am J Obstet Gynecol* 1999;181:202-206.
21. Penney GC, Mair G, Pearson DW. The relationship between birth weight and maternal glycated haemoglobin (HbA_{1c}) concentration in pregnancies complicated by Type 1 diabetes. *Diabet Med* 2003;20:162-166.
22. Beaty TH, Skjaerven R, Breazeale DR, Liang KY. Analyzing sibship correlations in birth weight using large sibships from Norway. *Genet Epidemiol* 1997;14:423-433.
23. Tanner JM, Lejarraga H, Turner G. Within-family standards for birth-weight. *Lancet* 1972;2:193-197.

24. Davis R, Woelk G, Mueller BA, Daling J. The role of previous birthweight on risk for macrosomia in a subsequent birth. *Epidemiology* 1995;6:607-611.

25. Odegard RA, Vatten LJ, Nilsen ST, Salvesen KA, Austgulen R. Preeclampsia and fetal growth. *Obstet Gynecol* 2000;96:950-955.

26. Steer PJ, Little MP, Kold-Jensen T, Chapple J, Elliott P. Maternal blood pressure in pregnancy, birth weight, and perinatal mortality in first births: prospective study. *BMJ* 2004;329:1312.

27. Xiong X, Demianczuk NN, Saunders LD, Wang FL, Fraser WD. Impact of preeclampsia and gestational hypertension on birth weight by gestational age. *Am J Epidemiol* 2002;155:203-209.

28. Xiong X, Fraser WD. Impact of pregnancy-induced hypertension on birthweight by gestational age. *Paediatr Perinat Epidemiol* 2004;18:186-191.

29. Tamborlane WV, Champion MC, Rizza RA, Service FJ, Bergenstal RM. Observations on control of glycemia with conventional insulin therapy or continuous subcutaneous insulin infusion. *Diabetes 34 Suppl* 1985;3:22-26.

30. Kloosterman GJ. On intra-uterine growth. *Int J Gynecol Obstet* 1970;8:895-912.

31. Mulik V, Usha Kiran TS, Bethal J, Bhal PS. The outcome of macrosomic fetuses in a low risk primigravid population. *Int J Gynaecol Obstet* 2003;80:15-22.

32. Stotland NE, Caughey AB, Breed EM, Escobar GJ. Risk factors and obstetric complications associated with macrosomia. *Int J Gynaecol Obstet* 2004;87:220-226.

33. Goldman JA, Dicker D, Feldberg D, Yeshaya A, Samuel N, Karp M. Pregnancy outcome in patients with insulin-dependent diabetes mellitus with preconceptional diabetic control: a comparative study. *Am J Obstet Gynecol* 1986;155:293-297.

34. Rosenn B, Siddiqi TA, Miodovnik M. Normalization of blood glucose in insulin-dependent diabetic pregnancies and the risks of hypoglycemia: a therapeutic dilemma. *Obstet Gynecol Surv* 1995;50:56-61.

35. Little RE. Mother's and father's birthweight as predictors of infant birthweight. *Paediatr Perinat Epidemiol* 1987;1:19-31.

36. Ehrenberg HM, Mercer BM, Catalano PM. The influence of obesity and diabetes on the prevalence of macrosomia. *Am J Obstet Gynecol* 2004;191:964-968.

37. Schaefer-Graf UM, Heuer R, Kilavuz O, Pandura A, Henrich W, Vetter K. Maternal obesity not maternal glucose values correlates best with high rates of fetal macrosomia in pregnancies complicated by gestational diabetes. *J Perinat Med* 2002;30:313-321.

38. Kerssen A, Evers IM, Valk de 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* 2003;13:309-313.

39. Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Clin Chem* 2002;48:436-472.

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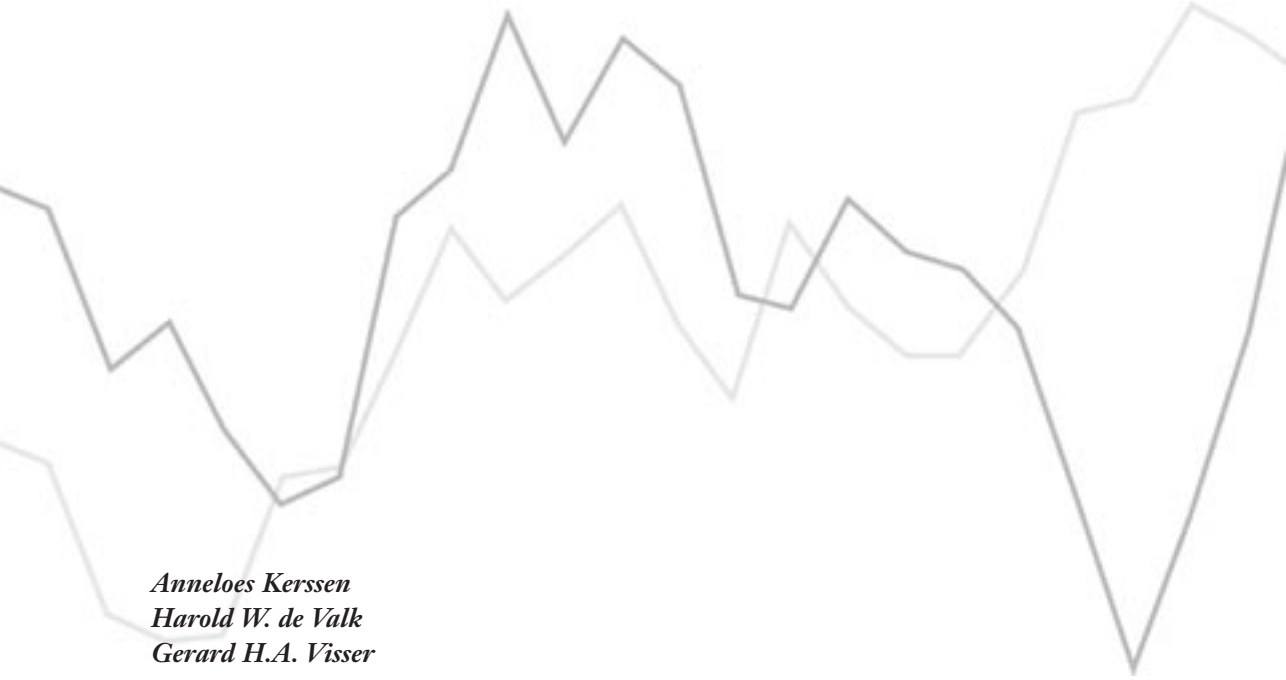
Diurnal glucose profiles during pregnancy in women with type 1 diabetes mellitus;

relations with infant birth weight



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Abstract

Objective Despite modern methods of treatment, pregnancies of women with type 1 diabetes are still complicated by macrosomia of the infant (birth weight ≥90th centile). To obtain a more complete image of diurnal glucose profiles during pregnancies of women with diabetes and to assess the relation between these glucose profiles and infant birth weight, a continuous glucose monitoring system (CGMS) was used in each trimester of the pregnancy.

Methods Fifty pregnant women with type 1 diabetes and twelve healthy pregnant women were asked to use the CGMS each trimester of pregnancy. The diurnal glucose profiles of the healthy women, the women with diabetes with a normal weight infant and those with a macrosomic infant were compared using repeated measurement analyses.

Results Women with diabetes invariably had higher glucose levels than healthy pregnant women. Sixty percent of the women with diabetes gave birth to a macrosomic infant of which 40% had elevated growth parameters on ultrasound ≤30 weeks of gestation. All of these early macrosomic infants became severely macrosomic (birth weight ≥97.7th centile). The mothers of these infants had significantly higher glucose levels in the second trimester of pregnancy ($p<0.05$). Women with diabetes who gave birth to a macrosomic infant had significant higher within-day glucose variability in the third trimester of pregnancy than women with normal weight infants ($p<0.05$).

Conclusion Pregnant women with type 1 diabetes at risk of giving birth to a severely macrosomic infant may be identified by elevated glucose levels in the second trimester and increased glucose variability in the third trimester of pregnancy.

Introduction

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 (frequent self-monitoring of blood glucose levels combined with multiple injection schedules or insulin pumps) [2-6] and despite the maintenance of HbA_{1c}-levels within the limits advised in international guidelines.[2,7]
Macrosomia of the infant (birth weight $\geq 90^{th}$ centile) is the most frequent of these complications.[2-6,8,9] It is a serious complication as it is associated with increased direct and late morbidity of both mother and child.[10-12] Instrumental delivery, caesarean section, shoulder dystocia, postpartum hemorrhage and perineal laceration rates are elevated in women whose infant is macrosomic.[10-13] Macrosomic infants have an increased risk of low apgar scores (<4) and prolonged admission to the special baby care unit.[10-12,14]
It has been shown that the macrosomia rate is positively related to glycaemic control.[15-18] Discrepancy, however, exists concerning the trimester of pregnancy in which tight glucose regulation is considered the most important. A second obstacle in these studies is that glycaemic control is 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. It has been shown that during pregnancy post-prandial glucose peaks of women with type 1 diabetes are particularly high and that these peaks are not monitored on routine testing.[19,20] It is plausible that the persistent high rate of infant macrosomia is due to unnoticed intermittent hyperglycaemia.
A novel method for the continuous monitoring of glycaemic control is the Continuous Glucose Monitoring System (CGMS). 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 mellitus in all three trimesters of the pregnancy. We aimed at establishing the relationship between the diurnal glucose profiles, HbA_{1c}-levels and birth weight of the infants born to these women.

Methods

The Continuous Glucose Monitoring System

The Continuous Glucose Monitoring System (CGMS) is a device that measures glucose levels in the extra cellular fluid of the abdominal subcutaneous tissue and stores values in a range of 2.2-22.2 mmol/l every 5 minutes during 72 hours. The

CGMS consists of three components: a sterile disposable glucose sensor, a glucose monitor and a connecting cable. The sensor consists of a thin, one centimetre long flexible polyurethane tube that houses the glucose-sensing electrode. The sensor measures interstitial glucose as an electrical potential created by the reaction of glucose oxidase with glucose. The sensor signal is acquired every 10 seconds and an average of the acquired signals is saved in the monitor every 5 minutes providing 288 readings in 24 hours. Besides interstitial glucose levels, the monitor stores event markers for meals, insulin injections and exercise.
The electrical readings acquired by the sensor are converted into glucose levels (mmol/l) when the data are downloaded from the monitor to a personal computer. To be able to determine a calibration factor, at least four finger stick blood glucose levels need to be entered into the monitor each 24 hours.
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 day. 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%. 21 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.

Patients and Methods

From December 2001 through June 2004 fifty pregnant women with type 1 diabetes mellitus were recruited from the obstetrical outpatient clinic of the University Medical Centre Utrecht, The Netherlands. Four women were excluded from the analyses: two were pregnant with twins and two had a spontaneous abortion. This report concerns the analyses of the remaining 46 patients.
As a control group, twelve healthy pregnant women were recruited (See Chapter 4). All study subjects gave written informed consent before entering the study.
The study subjects (diabetic and non-diabetic) were asked to use the CGMS three times during the 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.
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).
Macrosomia was defined as a birth weight ≥90th centile after correction for gender, parity and gestational age according to the Dutch growth charts.[22] Fetal growth was measured fortnightly using ultrasound. Retrospectively, the ultrasound reports

of the infants that were macrosomic were evaluated and a difference was made between infants with early macrosomia (fetal growth parameters ≥95th centile ≤30 weeks of gestation) and late macrosomia (fetal growth parameters ≥95th centile >30 weeks of gestation).
HbA_{1c}-levels were measured within one week after each continuous glucose measurement. In 54% of the patients HbA_{1c}-levels were also obtained six to eight weeks after the CGMS measurement. Comparison of the two HbA_{1c}-levels showed a correlation coefficient of 0.81 ($p<0.001$). A paired T-test showed that HbA_{1c}-levels obtained one week or six to eight weeks after the CGMS measurement were not significantly different ($p=0.269$). HbA_{1c}-levels determined within one week after the CGMS measurement were therefore found fit to use in the present study.

Analysis

In the women with type 1 diabetes mellitus, maternal and neonatal descriptives were compared between women with normal weight infants, women with a late macrosomic infant and women with an early macrosomic infant using Kruskal-Wallis or Chi-square statistics.
For each trimester of the pregnancy the median glucose levels for each hour of the day of each group of subjects (healthy women and the three diabetic subgroups) were calculated. For each trimester of the pregnancy the 24-point diurnal glucose profiles of the four study groups were compared using repeated measurement analyses.
The relationship between the HbA_{1c}-levels in the first, second and third trimester of the pregnancy and infant birth weight was established using Pearson correlation. Infant birth weight was expressed as percentage of the population mean corrected for gender and gestational age.
For statistical analyses $p<0.05$ was considered significant.

Results

Use of the CGMS

Not all women completed the 72 hours of CGMS registration due to technical reasons or the inconvenience of using the CGMS combined with the use of an insulin pump. Therefore, the first 24-hours of each CGMS measurement that best met the manufacturers accuracy criteria were used for the analyses.
In the diabetic study group, 26 patients used the CGMS three times during the pregnancy. The patients who did not complete three CGMS measurements were either included after the first trimester, delivered before the last CGMS measurement took place or did not complete the study (*Table 1*). All but one of the patients who did not complete the study (n=10) used continuous subcutaneous insulin infusion as the method of insulin administration and found the use of two devices

attached to the (growing) belly too inconvenient. A total of 106 measurements days were analysed.

Table 1. CGMS measurements

	n
First trimester measurements	40
- included after 12 weeks of gestation	6
Second trimester measurements	36
- included after 28 weeks of gestation	4
- failure to complete	6
Third trimester measurements	30
- delivered before measurement	5
- failure to complete	10

Table 2. Maternal descriptives

	n (%)
Parity	
0	23 (50)
1	18 (39)
2	4 (9)
3	1 (2)
Mode of delivery	
Caesarian section	29 (63)
Elective	23
Emergency	6
Operative Vaginal Delivery	3 (7)
Forceps	1
Vacuum extractor	2
Normal vaginal delivery	14 (30)
Gestational age at delivery	
< 37 weeks	14 (31)
37 to 40 weeks	30 (65)
≥ 40 weeks	2 (4)

Pregnancy outcome of women with diabetes

Median age (± interquartile range) of the women with type 1 diabetes at birth of the infant was 34.1±6.5 years. Twenty-three patients (50%) were pregnant for the first time (*Table 2*). Two patients had pre-existent hypertension and one patient developed pre-eclampsia. One patient experienced a hypoglycaemic coma in the first trimester of pregnancy. Sixty-three percent of the patients were delivered by caesarean section and 31% delivered before 37 weeks of gestation (*Table 2*).
One severely macrosomic infant died a few hours after birth due to asphyxia during labour. Four infants were born with a congenital malformation. In one case the congenital malformation could be attributed to the use of valproic acid early in the pregnancy. In the remaining three cases (6.5%) the malformations were attributed to the diabetes of the mother. The four women who gave birth to an infant with a congenital malformation were excluded from the analysis.
Sixty percent (n=25) of the infants were macrosomic (birth weight ≥p90). Of the macrosomic infants, 40% (n=10) became ultrasonically macrosomic before 30 weeks

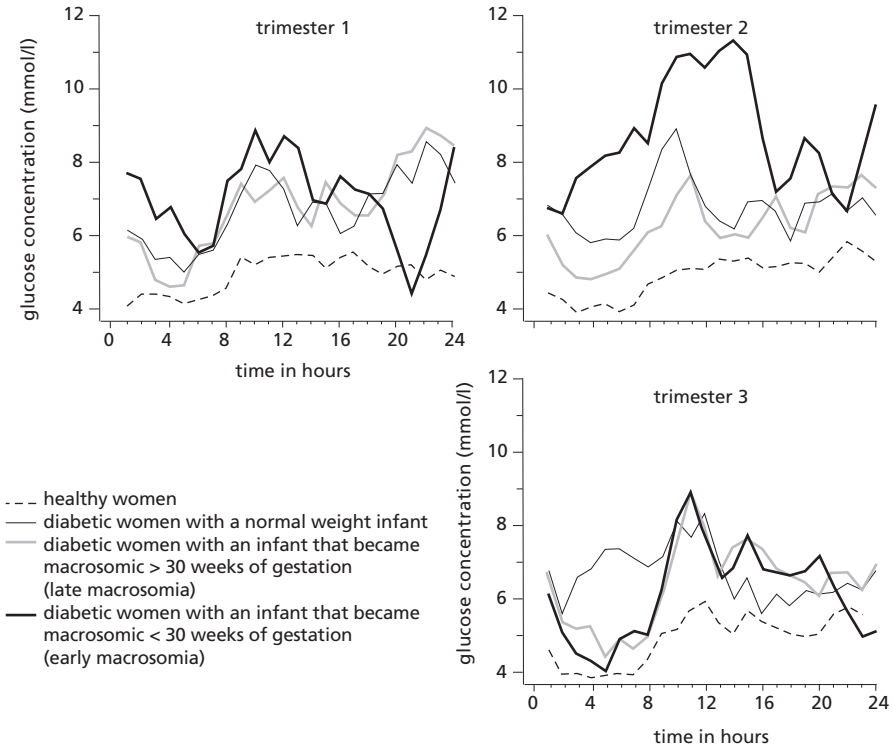


Figure 1. Median diurnal glucose profiles (midnight to midnight) in each trimester of pregnancy of healthy women and of diabetic women after categorization based on infant birth weight.

Table 3 Maternal and neonatal desciptives of normal weight, late macrosomic and early macrosomic infants of women with type 1 diabetes mellitus

	Birth weight			p
	< p90	≥p90 late macrosomia	≥p90 early macrosomia	
Number (n)	17	15	10	
Maternal descriptives				
Maternal age (year)	35.0 ± 3.6	34.5 ± 5.6	33.0 ± 4.6	0.519
Prepregnancy BMI (kg/m^2)	24.6 ± 5.0	26.3 ± 6.8	25.8 ± 4.5	0.718
Duration of diabetes (year)	13.0 ± 10.2	17.0 ± 8.2	20.0 ± 7.2	0.141
Method of insulin administration (n/n)	mit / csii 7 / 10	mit / csii 6 / 9	mit / csii 7 / 3	0.492
Type of insulin (n/n)	human / analoge 11 / 6	human / analoge 10 / 5	human / analoge 6 / 4	0.681
White classification (n/n)	B / C / D / F 9 / 4 / 3 / 1	B / C / D / F 4 / 6 / 5 / 0	B / C / D / F 0 / 6 / 3 / 1	0.127
Neonatal descriptives				
Gender (n/n)	male / female 8 / 9	male / female 10 / 5	male / female 4 / 6	0.362
Gestational age at birth (weeks)	38.0 ± 1.6	38.0 ± 1.8	37.1 ± 1.0	0.257
Birth weight (g)	3092 ± 534	3881 ± 254	4230 ± 378	0.000*
Birth weight centile	52 ± 23	95 ± 2	98 ± 0.3	0.000*
Hypoglycaemia (n)	yes / no 9 / 8	yes / no 10 / 5	yes / no 7 / 2	0.526

*Significant with p<0.001

of gestation (early macrosomia). All of the early macrosomic infants had a birth weight ≥p97.7 (severe macrosomia). Of the 14 infants that became macrosomic on ultrasound after 30 weeks of gestation only three were severely macrosomic at birth (21%). There was no significant difference in maternal age, pre-pregnancy BMI, duration of diabetes, method of insulin administration, type of insulin and white classification between the normal weight, the late macrosomic and the early macrosomic infants (*Table 3*). Of the infant characteristics only birth weight and birth weight centile was significantly different between the normal weight, the late macrosomic and the early macrosomic infants (*Table 3*).

Diurnal glucose profiles

Figure 1 shows the diurnal glucose profiles of healthy women and of women with diabetes who gave birth to a normal weight infant, a late macrosomic infant or an early macrosomic infant in the first, second and third trimester of pregnancy. In all three trimesters of the pregnancy the diurnal glucose levels of the healthy women were significantly lower than those of the women with diabetes ($p<0.01$). The median diurnal glucose levels of the women with diabetes who gave birth to an early macrosomic infant were significantly higher during the second trimester of pregnancy than those of the women with diabetes who gave birth to a normal weight or a late macrosomic infant ($p<0.05$). The interquartile range of the diurnal glucose profile in the second trimester of pregnancy of the women who gave birth to an early macrosomic infant is given in *Figure 2*. At least 75% of the women with an early macrosomic infant had glucose levels during the day that were higher than those of the women who gave birth to a late macrosomic or normal weight infant. In the third trimester, within-day glucose variability was significantly higher in women with a macrosomic infant (late and early) than in women with a normal weight infant ($p<0.05$)

HbA_{1c}-levels of women with diabetes

Figure 3 shows that the relationship between HbA_{1c}-levels and infant birth weight was only significant during the third trimester of pregnancy. The median HbA_{1c}-level in the third trimester of pregnancy was significantly higher in women who gave birth to an early macrosomic infant than in healthy women or women who gave birth to a normal weight infant, but did not exceed 7.0% (*Table 4*).

Table 4. Median and interquartile range of HbA_{1c}-levels (%) in each trimester of pregnancy in healthy women and women with type 1 diabetes mellitus who gave birth to a normal weight infant, a late macrosomic infant or an early macrosomic infant.

	Healthy women	Women with type 1 diabetes mellitus			Significance†
		Normal birth weight	Late macrosomia	Early macrosomia	
Trimester 1	5.3 ± 0.2	6.0 ± 0.7	6.3 ± 0.8	6.8 ± 1.3	0.398
Trimester 2	5.4 ± 0.2	6.3 ± 0.8	6.1 ± 1.0	6.9 ± 0.6	0.125
Trimester 3	5.6 ± 0.4	6.0 ± 0.9	6.2 ± 0.8	7.0 ± 0.9	0.020*

* significant with $p<0.05$

† Comparison of HbA_{1c}-levels between the different groups of women with diabetes

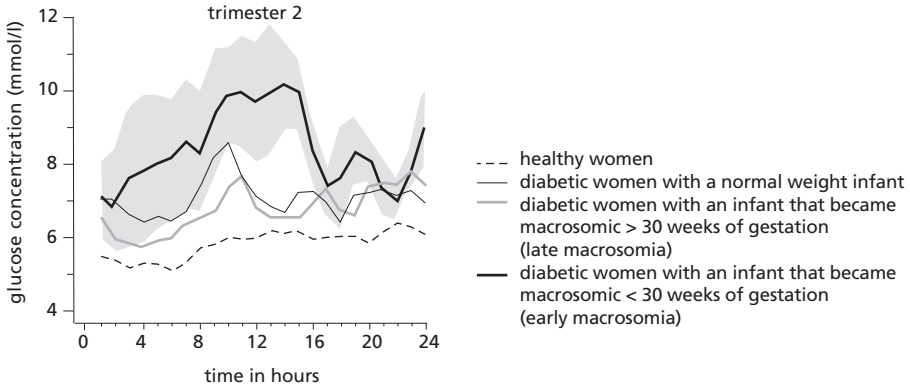


Figure 2. Median diurnal glucose profiles in the second trimester of pregnancy of healthy women and of diabetic women after categorization based on infant birth weight. The IQR of the glucose levels of the diabetic women who gave birth to an early macrosomic infant is given (the shaded area).

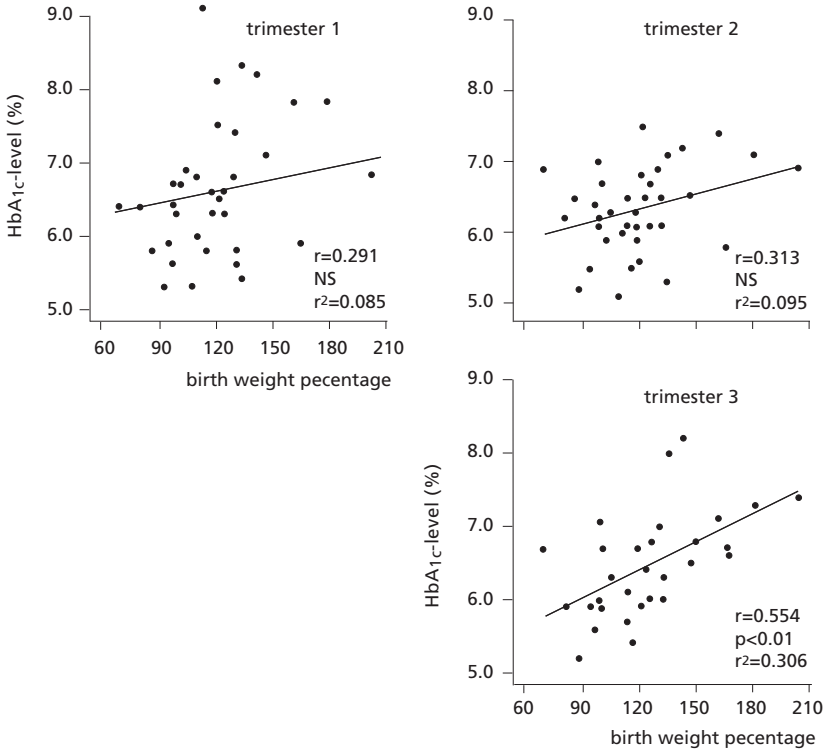


Figure 3. Relation between HbA_{1c}-level and birth weight expressed as percentage of population mean corrected for gender and gestational age.

Discussion

This study shows a very high percentage of fetal macrosomia (60%) in women with type 1 diabetes, despite 'safe' HbA_{1c}-values (≤7.0%;[7]) in most of the cases. The infants who were extremely macrosomic 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 macrosomic infants. These findings indicate that severe macrosomia starts relatively early in pregnancy and is likely to be caused by elevated maternal glucose levels. Macrosomia is a serious complication as it is associated with short term complications such as increased rates of caesarean section, shoulder dystocia and neonatal hypoglycaemia.[10-12,23-25] Long term complications for the infant include increased risks for obesity, diabetes and breast carcinoma later in life.[26,27]

In 1967 Pedersen introduced the concept of maternal hyperglycemia which reportedly increases the fetal secretion of insulin which in turn may cause fetal macrosomia.[28] 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.[29,30] Maternal HbA_{1c}-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.[9,31,32] In this study HbA_{1c}-levels during the first and second trimester explained 8-10% of the variance in birth weight and third trimester HbA_{1c}-levels explained 30% of the variance. Other studies indicate a much lower explained variance near term.[32,33] 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.[31,34] This suggests that post-prandial glycaemia rather than basal or mean glycaemia influences fetal growth and size at birth, which is in agreement with our data (*Figure 1*).

Recently it has been shown that HbA_{1c}-levels do not correlate well with 24h glucose profiles as measured with the CGMS.[35] This may explain the poor correlation between HbA_{1c}-levels and infant birth weight. Moreover, it has also been shown that post-prandial glucose peaks may not be detected by routine glucose testing.[20] 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.[36] It is a weakness of the present study that only one 24h glucose profile could be included per trimester

of pregnancy. Our data should be repeated by a study in which more often 24h profiles are measured, especially during the second trimester of pregnancy. During the third trimester of pregnancy glucose values were not higher in the women who gave birth to a macrosomic infant (early and late) as compared to the glucose profiles of women with a normal weight infant. However, the within-day variability was significantly higher in the women with a macrosomic infant. This suggests that also glucose variability plays a role in the aetiology of fetal macrosomia. Sudden increases in maternal glucose levels lead to sudden increases in fetal insulin level, which besides normalising glucose levels, may act as a growth hormone.

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.[37,38] 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 macrosomia, which is already evident before 30 weeks of gestation. To prevent excessive intra-uterine growth of these infants, glucose regulation should be tightened, especially during the second trimester of pregnancy.

References

1. Diabetes care and research in Europe: the Saint Vincent declaration. *Diabet Med* 1990;7:360.
2. Evers IM, de Valk HW, Visser GHA. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. *BMJ* 2004;328:915.
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* 1997;315:275-278.
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* 1997;315:279-281.
5. Penney GC, Mair G, Pearson DW. Outcomes of pregnancies in women with type 1 diabetes in Scotland: a national population-based study. *BJOG* 2003;110:315-318.
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* 2002;19:216-220.
7. Preconception care of women with diabetes. Diabetes Care 2004;27 Suppl 1:S76-78.
8. Berk MA, Mimouni F, Miodovnik M, Hertzberg V, Valuck J. Macrosomia in infants of insulin-dependent diabetic mothers. *Pediatrics* 1989;83:1029-1034.
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* 2002;45:1484-1489.

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* 2003;111:9-14.

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* 2003;188:1372-1378.

12. Meshari AA, De Silva S, Rahman I. Fetal macrosomia--maternal risks and fetal outcome. *Int J Gynaecol Obstet* 1990;32:215-222.

13. Stotland NE, Caughey AB, Breed EM, Escobar GJ. Risk factors and obstetric complications associated with macrosomia. *Int J Gynaecol Obstet* 2004;87:220-226.

14. Mulik V, Usha Kiran TS, Bethal J, Bhal PS. The outcome of macrosomic fetuses in a low risk primigravid population. *Int J Gynaecol Obstet* 2003;80:15-22.

15. 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* 1987;156:1089-1095.

16. Page RC, Kirk BA, Fay T, Wilcox M, Hosking DJ, Jeffcoate WJ. Is macrosomia associated with poor glycaemic control in diabetic pregnancy? *Diabet Med* 1996;13:170-174.

17. 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* 1997;25:488-497.

18. 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* 2000;23:1494-1498.

19. Jovanovic-Peterson L, Peterson CM, Reed GF, Metzger BE, Mills JL, Knopp RH, Aarons JH. Maternal postprandial glucose levels and infant birth weight: the Diabetes in Early Pregnancy Study. The National Institute of Child Health and Human Development--Diabetes in Early Pregnancy Study. *Am J Obstet Gynecol* 1991;164:103-111.

20. 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* 1999;16:702-706.

21. Mastrototaro J. The MiniMed Continuous Glucose Monitoring System (CGMS). *J Pediatr Endocrinol Metab* 1999;12 Suppl 3:751-758.

22. Kloosterman GJ. On intra-uterine growth. *Int J Gynecol Obstet* 1970;8:895-912.

23. Cousins L. Pregnancy complications among diabetic women: review 1965-1985. *Obstet Gynecol Surv* 1987;42:140-149.

24. 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* 1991;165:831-837.

25. 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* 2002;187:913-917.

26. Van Assche FA, Holemans K, Aerts L. Fetal growth and consequences for later life. *J Perinat Med* 1998;26:337-346.

27. Samaras TT, Elrick H, Storms LH. Birthweight, rapid growth, cancer, and longevity: a review. *J Natl Med Assoc* 2003;95:1170-1183.

28. 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: 128-137.

29. Weiss PA, Lichtenegger W, Winter R, Purstner P. Insulin levels in amniotic fluid. Management of pregnancy in diabetes. *Obstet Gynecol* 1978;51:393-398.

30. 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* 1997;49:97-105.

31. 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* 1996;103:427-433.

32. Johnstone FD, Mao JH, Steel JM, Prescott RJ, Hume R. Factors affecting fetal weight distribution in women with type I diabetes. *BJOG* 2000;107:1001-1006.

33. Gold AE, Reilly R, Little J, Walker JD. The effect of glycemic control in the pre-conception period and early pregnancy on birth weight in women with IDDM. *Diabetes Care* 1998;21:535-538.

34. Parfitt VJ, Clark JD, Turner GM, Hartog M. Maternal postprandial blood glucose levels influence infant birth weight in diabetic pregnancy. *Diabetes Res* 1992;19:133-135.

35. Kerssen A, Evers IM, Valk de 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* 2003;13:309-313.

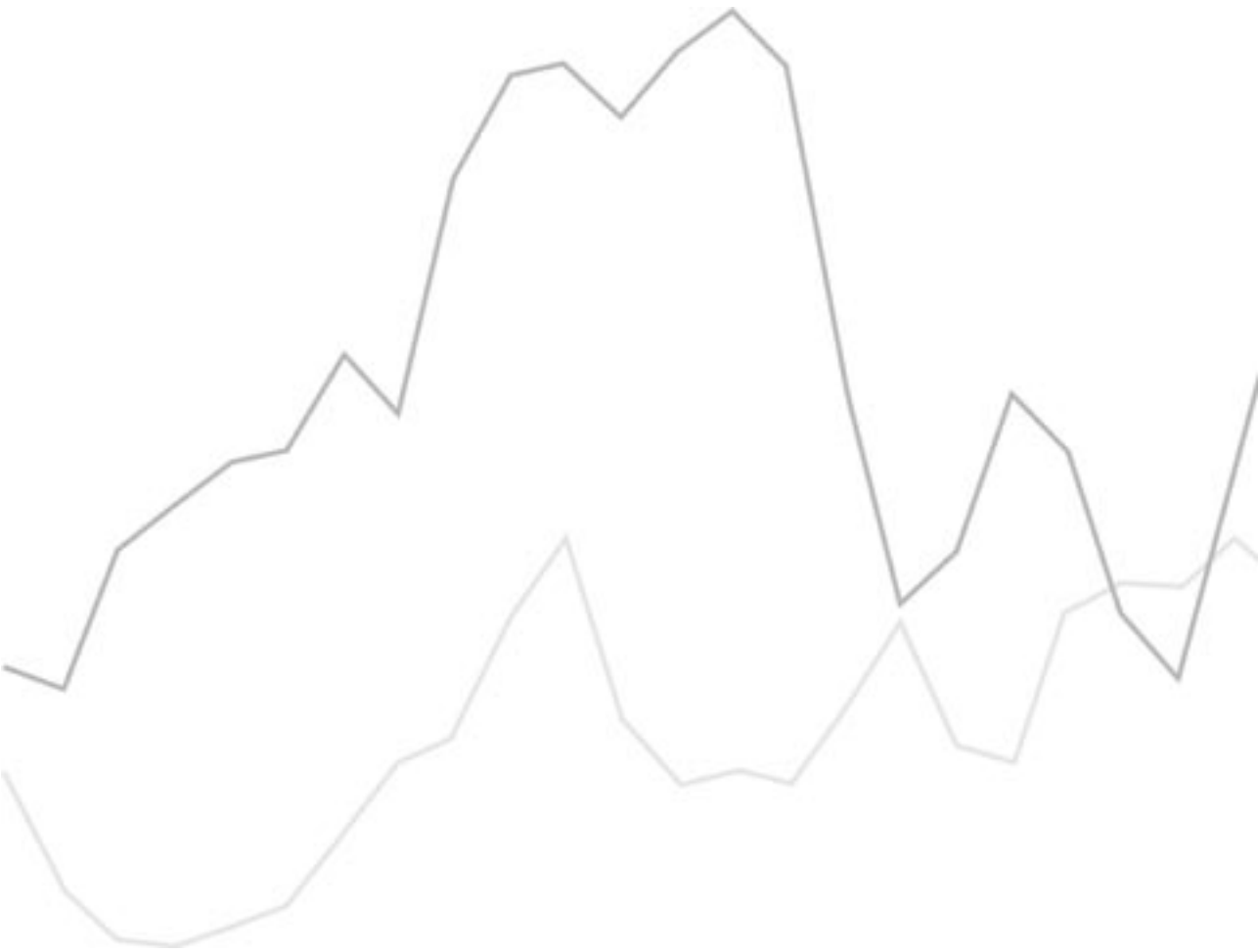
36. Kerssen A, de Valk HW, Visser GHA. The Continuous Glucose Monitoring System during pregnancy of women with type 1 diabetes mellitus: accuracy assessment. *Diabetes Technol Ther* 2004;6:645-651.

37. 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* 1995;85:417-422.

38. Evers IM, ter Braak EW, de Valk HW, van Der Schoot B, Janssen N, Visser GHA. Risk indicators predictive for severe hypoglycemia during the first trimester of type 1 diabetic pregnancy. *Diabetes Care* 2002;25:554-559.

11

Summary and Conclusions



Summary

In 1989 representatives of Government Health Departments and patient organizations from all European countries unanimously agreed upon recommendations concerning diabetes care in Europe. One of the recommendations stated in this Saint Vincent Declaration is that the treatment in a pregnant woman with diabetes should be aimed at achieving a pregnancy outcome that approximates that of a non-diabetic woman.[1] Meanwhile, several studies have shown that this target is currently far from being reached, with perinatal complication rates three to six times that of background populations.[2-7] It is remarkable that these complication rates remain high despite the achievement of 'safe' diabetic control as noted in international guidelines.[8] These guidelines state that complication rates should be equal to those seen in non-diabetic women when HbA_{1c}-levels are within 1% above the upper limit of normal, but apparently that is not the case.[8]
We hypothesised that intermittent hyperglycaemia is the main cause of the problems seen during pregnancies of women with type 1 diabetes mellitus. It is likely that such intermittent hyperglycaemic episodes are not reflected by HbA_{1c}-levels since these give information on glycaemic control over a two to three-month period.[9] Previous studies have shown that during pregnancy post-prandial glucose peaks of women with type 1 diabetes are particularly high and that these peaks are not monitored on routine testing.[10,11]
A novel device for the continuous monitoring of glucose levels is the Continuous Glucose Monitoring System (CGMS). With this system it is possible to monitor glucose levels in the home setting every five minutes uninterrupted for 72 hours. With the availability of the CGMS the opportunity arose to observe diurnal glucose profiles in pregnant women with type 1 diabetes mellitus and to assess the relation between these glucose profiles and perinatal outcome.

The CGMS measures glucose levels through electrochemical detection in the interstitial fluid of the abdominal subcutaneous tissue. Research has shown that interstitial glucose levels are 20-50% lower than blood glucose levels.[12] Calibration of the CGMS with capillary glucose levels enables the system to correct for this difference. However, in non-pregnant diabetic subjects the clinical performance of the CGMS has occasionally been reported unsatisfactory.[13-15] In *chapter 2* we determined the accuracy of the CGMS in pregnant women with type 1 diabetes. Two hundred and thirty nine fingerstick blood glucose values of fifteen patients were related to simultaneously measured CGMS glucose values. The correlation coefficient between these values was 0.94 ($p<0.001$). Ninety-four percent of the data pairs fell in the clinically acceptable zones of the Clarke error grid. The Clarke error-grid describes the accuracy of glucose measurement systems over the entire range of glucose values taking into account the clinical significance of differences between these measurement systems.[16] The clinically important differences in

glucose values measured with the CGMS and with finger stick measurement were all in the hypoglycaemic range.
In *chapter 3* the reproducibility of the CGMS was assessed. Five pregnant women with type 1 diabetes used two CGMS devices simultaneously. The correlation coefficient between simultaneously measured data was 0.94 ($p<0.001$). Almost 80% of the data pairs could be classified in the same glucose range (normoglycaemia, hypoglycaemia or hyperglycaemia). In 81% of the non-concordant pairs, one glucose value was classified in the hypoglycaemic range and the other in the normoglycaemic range.
We concluded that the accuracy and reproducibility of the CGMS in pregnant women with type 1 diabetes is adequate. The small degree of error found in the hypoglycaemic range is concordant with the findings in non-pregnant diabetic patients.[15,17,18] As there was no consistent difference between the glucose values measured with the simultaneously used CGMS devices, the cause of the errors is most likely technical (the measurement of electrical potential created by the reaction of glucose oxidase with glucose) or analytical (conversion of the electrical readings into glucose levels).
Thus, the CGMS is a useful device in the management of type 1 diabetes in pregnant women but should only be considered a supplementary tool as it occasionally misleads in the hypoglycaemic range.

A major obstacle in the treatment of pregnant women with type 1 diabetes is the lack of an internationally established definition of normoglycaemia during pregnancy. In *chapter 4* diurnal glucose levels were measured in twelve healthy pregnant women. These women used the CGMS once in each trimester of pregnancy and once after pregnancy. Nighttime and fasting glucose levels decreased throughout pregnancy and were regularly less than the lower limit of normoglycaemia outside pregnancy (3.9 mmol/l). Post-prandial glucose values increased throughout pregnancy and regularly exceeded the upper limit of normoglycaemia outside pregnancy (7.8 mmol/l).
The decrease in nocturnal glucose levels is most likely due to the fact that late pregnancy can be considered a catabolic condition.[19] During late pregnancy, liver glycogen stores are depleted and therefore gluconeogenesis is enhanced.[20] This, combined with an increased utilization of glucose, leads to hypoglycaemia, which is especially manifest after a period of fasting (nighttime).[21,22]
The increase in post-prandial glucose levels may be explained by a 50% decrease in peripheral insulin sensitivity in the third trimester of pregnancy.[23-25] This leads to a decrease in glucose tolerance in late normal pregnancy. The increased maternal post-prandial glucose levels as found in this trimester are thought to be needed to compensate for the increasing glucose needs of the growing fetus.[26,27]
Our findings may be of help in establishing the aim of treatment strategies in pregnant women with diabetes. Treatment strategies in pregnant women with

diabetes should be aimed at avoiding hyperglycaemia. However, since incidental post-prandial hyperglycaemia in the third trimester of pregnancy appears to be a normal phenomenon in healthy women, occasional post-prandial glucose elevations (<10.0 mmol/l) are acceptable. Downside of the tightening of glycaemic control in pregnant women with diabetes is an increase in hypoglycaemia risk.[28] This risk is likely to be highest during the night and early morning hours when, in healthy women, glucose levels in the hypoglycaemic range are normal. The treatment of pregnant women with diabetes should be aimed at finding a balance between tight glycaemic control and hypoglycaemia risk.

According to the American Diabetes Association, HbA_{1c}-levels within 1% above the upper limit of normal range (*i.e.* ≤7.0%) are considered 'safe' during pregnancy. However, population studies still show increased complication rates when HbA_{1c}-values are in between 6.0 and 7.0%.[6] In *chapter 5* we compared continuous glucose profiles of women with type 1 diabetes with HbA_{1c}-levels in the first trimester of pregnancy. CGMS glucose recordings were obtained in 13 women between 7 and 15 weeks of gestation. Nine patients had HbA_{1c}-levels ≤7.0% while up to 41% of the readings in these patients were ≤3.9 mmol/l and up to 53% of the readings showed values ≥7.8 mmol/l. These findings demonstrate that HbA_{1c}-levels do not accurately reflect the complexities of glycaemic control in women with type 1 diabetes. They also indicate that tight glycaemic control may only be accomplished when HbA_{1c}-levels are within the normal range (4.0-6.0%).
In *chapter 6* the accuracy of the limits of HbA_{1c}-levels currently used in international guidelines is further explored by relating the glucose levels of 185 CGMS measurement days of 43 patients to their HbA_{1c}-levels. The glucose levels measured with the CGMS were compared between patients with HbA_{1c}-levels 4.0-6.0% (normal range), 6.0-7.0% ('safe' range) and >7.0% (high range). In patients with HbA_{1c}-levels ≤6.0% glucose levels were significantly better than in patients with HbA_{1c}-levels >6.0%. Glucose levels in women with HbA_{1c}-levels 6.0-7.0% and >7.0% did not differ. These findings again indicate that treatment strategies of pregnant women with diabetes should be aimed at achieving HbA_{1c}-levels within the normal range (*i.e.* ≤6.0%).
To safely and effectively manage diabetes, daily self-monitoring of blood glucose levels (SMBG) is critical.[29-32] During pregnancy SMBG is recommended at least three times per day.[33] To assess the number of SMBG that have to be obtained daily to give an accurate idea of the glucose profile in pregnant women with diabetes, glucose levels measured with SMBG and with the CGMS were compared between patients with 4-5, 6-9 and ≥10 SMBG daily. The detection rate of hyperglycaemic episodes was 100% if patients measured their glucose values ≥10 times daily. The hypoglycaemia detection rate improved significantly when SMBG was performed ≥10 times daily but 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.[34,35] It is also conceivable that in case of symptomatic hypoglycaemia, patients will treat the hypoglycaemia before measuring their blood glucose level.
Thus, almost normal HbA_{1c}-levels are not good enough and 'safe' glycaemic control implies normoglycaemia. However, if one takes into account the increased risk of severe hypoglycaemia encountered in the strain for normoglycaemia, this may not always be considered 'safe' for the mother.[28,34,36,37] The risk and fear of a severe hypoglycaemic episode in a pregnant woman with diabetes often hampers the achievement of normoglycaemia.[28] To find the optimal balance between tight glycaemia and hypoglycaemia risk, accurate knowledge of daily glucose profiles is mandatory. In order to obtain this, patients should monitor themselves at least ten times per day. We realise that this may be difficult to achieve in clinical practice.

To achieve normoglycaemia, fine-tuning of insulin regimens is necessary. Adjustments in insulin regimens based on frequent SMBG or CGMS measurements are only feasible if day-to-day variability is limited and could even be harmful when day-to-day variability is large. In *chapter* 7 the degree of day-to-day variability in pregnant women with type 1 diabetes was studied and the consequences on treatment decisions was assessed. Thirty-one pregnant women with diabetes used the CGMS for two consecutive days. Based on visual inspection of the two-day glucose profiles, 55% of the patients were classified as having low day-to-day variability (Mean Absolute Difference 0.92-2.33 mmol/l) and 45% of the patients were classified as having high day-to-day variability (MAD 2.41-6.12 mmol/l). There was no difference in maternal age and BMI, duration of diabetes, number of self-monitored blood glucose levels, number of insulin injections, gestational age, nutrition, physical activity, White-classification, living with children and method of insulin administration between the patients with low or high day-to-day variability. Women with a low day-to-day variation had a lower within-day variation and a lower HbA_{1c}-level. High within-day variation often means alternation between post-prandial hyperglycaemia and pre-meal hypoglycaemia. Initially we hypothesised that the chance of these fluctuations occurring at the exact same time on two consecutive days is small due to variations in rhythm of meals, exercise, sleep, etc. However, the finding that mean MAD in the group of women with different daily activities is almost identical to the mean MAD of women with similar daily activities on the measurement days did not confirm this.
The difference in recommendation on treatment adjustment between day 1 and day 2 of the CGMS measurement was significantly higher in the high day-to-day variability group ($p<0.01$). This means that insulin adjustment based on the information of continuous glucose monitoring is hampered by day-to-day variability in about half the patients when they are monitored for two days.
In *chapter 8* the usefulness of three-day compared to two-day CGMS measurements was assessed. Evaluation of 36 three-day CGMS measurements showed that in 88%

of the patients with low day-to-day variability between day 1 and day 2 of the measurement, the glucose profile of the third measurement day did not differ from that of the previous two measurement days. Two days of continuous glucose measurement therefore seems to be enough for the identification of most patients with a low day-to-day variability and the adjustment of insulin regimens in these patients. In patients with high day-to-day variability between day 1 and day 2 of the measurement, 79% had a high variability between day 2 and day 3 of the measurement. In these patients the CGMS measurements can be used to increase the awareness of variations in glucose levels leading to the adjustment of eating habits and regularity of living pattern. It remains to be seen if a third day of measurement is necessary when the CGMS is used for this purpose. Technically it appeared difficult to obtain three successive technically accurate measurement days (in only 36 out of 100 measurements of 47 patients).
Day-to-day variability is a large obstacle in the treatment of pregnant women with diabetes and future research into explanatory factors such as stress, diabetic autonomic neuropathy and eating patterns should be performed. Measurements made with the CGMS can be of help in the adjustment of insulin regimens in about half of the pregnant women with type 1 diabetes. Two days of CGMS measurement is generally enough to differentiate between high and low day-to-day variability and treatment adjustments can be made in the latter group of patients.

As shown in chapters 5 and 6, HbA_{1c}-levels do not accurately reflect the complexities of glycaemic control and are poor predictors of perinatal complications in pregnant women with type 1 diabetes. The most frequent complication is macrosomia of the infant.[3,6,7,38] In the non-diabetic population, birth weight of older siblings has been shown to correlate with birth weight of younger siblings.[39,40] Reported correlations of sibling weight in the non-diabetic population are strong and predictive values range from 20 to 30%, whereas in women with type 1 diabetes HbA_{1c}-levels account for less than 10% of the variance found in birth weight of their infants.[7,39-41] In *chapter 9* the predictive value of sibling birth weight and mean HbA_{1c}-levels during pregnancy on macrosomia was assessed in women with type 1 diabetes. Analysis of 214 pregnancies in 107 women showed birth weight of the first born infant to be significantly related to birth weight of the second born infant, whereby 40 to 50% of the variation in birth weight of second born-infants could be explained by the birth weight of the first-born infant. Eighty-five percent of the women who gave birth to a macrosomic infant, had a macrosomic infant at subsequent birth.
Thus, in women with type 1 diabetes, birth weight of an earlier born infant and not HbA_{1c}-levels should be used to identify patients at risk of giving birth to a macrosomic infant. As macrosomia is associated with higher rates of a prolonged first and second stage of labour, an increased risk of instrumental vaginal delivery, shoulder dystocia, caesarean birth, third and fourth-degree perineal lacerations, postpartum

hemorrhage, prolonged hospital stay, Apgar score <4 and admission to the special care baby unit [42-44] it is important to adjust glucose regulation and obstetrical care to the needs of these high risk patients.

So far we have shown that the relation between HbA_{1c}-levels and infant birth weight is weak and that HbA_{1c}-levels do not accurately reflect glucose levels in pregnant women with type 1 diabetes. As a next step we assessed the relation between diurnal glucose profiles and infant birth weight. In *chapter 10* we showed that diurnal glucose profiles of women with diabetes who gave birth to a macrosomic infant were different from those who gave birth to a normal weight infant. Fifty pregnant women with type 1 diabetes and twelve healthy pregnant women (described in Chapter 4) used the CGMS once during each trimester of pregnancy. The women with diabetes invariably had higher glucose levels than the healthy women. Sixty percent of the women with diabetes gave birth to a macrosomic infant of which 40% had growth parameters ≥95th centile on ultrasound before 30 weeks of gestation (early macrosomia). All of the latter infants became severely macrosomic at birth (birth weight ≥97.7th centile). Of the infants whose growth parameters on ultrasound exceeded the 95th centile after 30 weeks of gestation (late macrosomia) only 21% became severely macrosomic at birth. The mothers of the early macrosomic infants had significantly higher glucose levels for most of the day during the second trimester of pregnancy compared to the women with normal weight or late macrosomic infants. The latter two groups of women had glucose levels within the normal range with the exception of a short period after breakfast. The mothers of macrosomic infants (early and late) all had significant higher within-day glucose variability in the third trimester of pregnancy than women who gave birth to a normal weight infant. HbA_{1c}-levels were only in the third trimester of pregnancy significantly related to infant birth weight. In all these women with diabetes, median HbA_{1c}-levels during pregnancy did not exceed the 'safe' range (6.0-7.0%).
Elevated glucose levels and glucose variability thus both play an important role in the aetiology of infant macrosomia in pregnancies of women with type 1 diabetes. Women at risk of giving birth to a severely macrosomic infant and thus at risk of a number of complications during and after labour,[42-44] may already be identified by elevated daytime glucose levels in the second trimester of pregnancy. Intensive monitoring of glucose values and insulin adjustment in case of high values, therefore, seems especially important during the second trimester of pregnancy, when the excessive growth of infants eventually born severely macrosomic apparently starts.

Conclusions and Recommendations

The Continuous Glucose Monitoring System (CGMS) is an accurate tool for additional glucose monitoring in pregnant women with type 1 diabetes mellitus. The occasional use of the CGMS during pregnancy in women with diabetes is of great help in increasing the awareness of variations in glucose levels leading to the adjustment of eating habits and regularity of living pattern. If day-to-day variations are stable, CGMS measurements might also be a useful aid for the adjustment of insulin regimens.

During pregnancy, the incidental fall of glucose values below the lower limit of normoglycaemia, especially during the night, and glucose values that exceed the upper limit of normoglycaemia, especially after breakfast in the third trimester, appear to be a normal phenomenon in healthy women.

HbA_{1c}-levels in pregnant women with type 1 diabetes do not adequately reflect the complexities of glycaemic control and HbA_{1c}-levels between 6.0 and 7.0% are not 'safe' during pregnancy. Treatment in these women should be aimed at achieving normal HbA_{1c}-levels. A balance between normoglycaemia and hypoglycaemia risk should be found.

Frequent self-monitoring of blood glucose levels rather than HbA_{1c}-levels should be the main indicators of glycaemic control on which treatment strategies are based and should be performed at least ten times a day.

Day-to-day glucose variability is a major obstacle in the treatment of pregnant women with diabetes and obstructs adequate fine-tuning of insulin regimens in about half the patients.

Sibling birth weight is a better predictor of macrosomia than HbA_{1c}-levels.

Women with type 1 diabetes who give birth to a severely macrosomic infant have higher glucose levels during the second trimester of pregnancy and higher glucose variability during the third trimester of pregnancy than women with diabetes who give birth to a normal weight infant. Tight glycaemic control, especially during the second trimester of pregnancy, seems of great importance to prevent the occurrence of severe macrosomia. Identification of women at high risk of giving birth to a macrosomic infant can be achieved by the knowledge of the patients obstetrical history and by frequent ultrasound measurements starting early in pregnancy.

References

1. Diabetes care and research in Europe: the Saint Vincent declaration. *Diabet Med* 1990;7:360.
2. 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* 1997;315:275-278.
3. 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* 1997;315:279-281.
4. 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* 2002;19:216-220.
5. Penney GC, Mair G, Pearson DW. Outcomes of pregnancies in women with type 1 diabetes in Scotland: a national population-based study. *BJOG* 2003;110:315-318.
6. Evers IM, de Valk HW, Visser GHA. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. *BMJ* 2004;328:915.
7. 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* 2002;45:1484-1489.
8. Preconception care of women with diabetes. *Diabetes Care* 2004;27 Suppl 1:S76-78.
9. Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Clin Chem* 2002;48:436-472.
10. Jovanovic-Peterson L, Peterson CM, Reed GF, Metzger BE, Mills JL, Knopp RH, Aarons JH. Maternal postprandial glucose levels and infant birth weight: the Diabetes in Early Pregnancy Study. The National Institute of Child Health and Human Development--Diabetes in Early Pregnancy Study. *Am J Obstet Gynecol* 1991;164:103-111.
11. 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* 1999;16:702-706.
12. Rebrin K, Steil GM, van Antwerp WP, Mastrototaro JJ. Subcutaneous glucose predicts plasma glucose independent of insulin: implications for continuous monitoring. *Am J Physiol* 1999;277:E561-571.
13. Metzger M, Leibowitz G, Wainstein J, Glaser B, Raz I. Reproducibility of glucose measurements using the glucose sensor. *Diabetes Care* 2002;25:1185-1191.
14. Guerci B, Floriot M, Bohme P, Durain D, Benichou M, Jellimann S, Drouin P. Clinical Performance of CGMS in Type 1 Diabetic Patients Treated by Continuous Subcutaneous Insulin Infusion Using Insulin Analogs. *Diabetes Care* 2003;26:582-589.
15. The accuracy of the CGMS in children with type 1 diabetes: results of the diabetes research in children network (DirecNet) accuracy study. *Diabetes Technol Ther* 2003;5:781-789.
16. Clarke WL, Cox D, Gonder-Frederick LA, Carter W, Pohl SL. Evaluating clinical accuracy of systems for self-monitoring of blood glucose. *Diabetes Care* 1987;10:622-628.
17. McGowan K, Thomas W, Moran A. Spurious reporting of nocturnal hypoglycemia by CGMS in patients with tightly controlled type 1 diabetes. *Diabetes Care* 2002;25:1499-1503.
18. Caplin NJ, O'Leary P, Bulsara M, Davis EA, Jones TW. Subcutaneous glucose sensor values closely parallel blood glucose during insulin-induced hypoglycaemia. *Diabet Med* 2003;20:238-241.
19. Herrera E. Metabolic adaptations in pregnancy and their implications for the availability of substrates to the fetus. *Eur J Clin Nutr* 2000;54 Suppl 1:S47-51.

20. Assel B, Rossi K, Kalhan S. Glucose metabolism during fasting through human pregnancy: comparison of tracer method with respiratory calorimetry. *Am J Physiol* 1993;265:E351-356.

21. Bleicher SJ, O'Sullivan JB, Freinkel N. Carbohydrate Metabolism in Pregnancy. V. The Interrelations of Glucose, Insulin and Free Fatty Acids in Late Pregnancy and Post Partum. *N Engl J Med* 1964;271:866-872.

22. Herrera E, Knopp RH, Freinkel N. Carbohydrate metabolism in pregnancy. VI. Plasma fuels, insulin, liver composition, gluconeogenesis, and nitrogen metabolism during late gestation in the fed and fasted rat. *J Clin Invest* 1969;48:2260-2272.

23. Catalano PM, Tyzbir ED, Roman NM, Amini SB, Sims EA. Longitudinal changes in insulin release and insulin resistance in nonobese pregnant women. *Am J Obstet Gynecol* 1991;165:1667-1672.

24. Catalano PM, Tyzbir ED, Wolfe RR, Calles J, Roman NM, Amini SB, Sims EA. Carbohydrate metabolism during pregnancy in control subjects and women with gestational diabetes. *Am J Physiol* 1993;264:E60-67.

25. Buchanan TA, Metzger BE, Freinkel N, Bergman RN. Insulin sensitivity and B-cell responsiveness to glucose during late pregnancy in lean and moderately obese women with normal glucose tolerance or mild gestational diabetes. *Am J Obstet Gynecol* 1990;162:1008-1014.

26. Homko CJ, Sivan E, Reece EA, Boden G. Fuel metabolism during pregnancy. *Semin Reprod Endocrinol* 1999;17:119-125.

27. Chiasson JL, el Achkar GG, Ducros F, Bourque J, Maheux P. Glucose turnover and gluconeogenesis during pregnancy in women with and without insulin-dependent diabetes mellitus. *Clin Invest Med* 1997;20:140-151.

28. 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* 1995;85:417-422.

29. Walford S, Gale EA, Allison SP, Tattersall RB. Self-monitoring of blood-glucose. Improvement of diabetic control. *Lancet* 1978;1:732-735.

30. Schiffrin A, Belmonte M. Multiple daily self-glucose monitoring: its essential role in long-term glucose control in insulin-dependent diabetic patients treated with pump and multiple subcutaneous injections. *Diabetes Care* 1982;5:479-484.

31. Espersen T, Klebe JG. Self-monitoring of blood glucose in pregnant diabetics. A comparative study of the blood glucose level and course of pregnancy in pregnant diabetics on an out-patient regime before and after the introduction of methods for home analysis of blood glucose. *Acta Obstet Gynecol Scand* 1985;64:11-14.

32. Lam KS, Ma JT, Chan EY, Yeung RT. Sustained improvement in diabetic control on long-term self-monitoring of blood glucose. *Diabetes Res Clin Pract* 1986;2:165-171.

33. Standards of medical care in diabetes. *Diabetes Care* 2004;27 Suppl 1:S15-35.

34. Hellmuth E, Damm P, Molsted-Pedersen L, Bendtson I. Prevalence of nocturnal hypoglycemia in first trimester of pregnancy in patients with insulin treated diabetes mellitus. *Acta Obstet Gynecol Scand* 2000;79:958-962.

35. Rayburn W, Piehl E, Jacober S, Schork A, Ploughman L. Severe hypoglycemia during pregnancy: its frequency and predisposing factors in diabetic women. *Int J Gynaecol Obstet* 1986;24:263-268.

36. Kimmerle R, Heinemann L, Delecki A, Berger M. Severe hypoglycemia incidence and predisposing factors in 85 pregnancies of type I diabetic women. *Diabetes Care* 1992;15:1034-1037.

37. Evers IM, ter Braak EW, de Valk HW, van Der Schoot B, Janssen N, Visser GHA. Risk indicators predictive for severe hypoglycemia during the first trimester of type 1 diabetic pregnancy. *Diabetes Care* 2002;25:554-559.

38. Berk MA, Mimouni F, Miodovnik M, Hertzberg V, Valuck J. Macrosomia in infants of insulin-dependent diabetic mothers. *Pediatrics* 1989;83:1029-1034.

39. Beaty TH, Skjaerven R, Breazeale DR, Liang KY. Analyzing sibship correlations in birth weight using large sibships from Norway. *Genet Epidemiol* 1997;14:423-433.

40. Tanner JM, Lejarraga H, Turner G. Within-family standards for birth-weight. *Lancet* 1972;2:193-197.

41. Johnstone FD, Mao JH, Steel JM, Prescott RJ, Hume R. Factors affecting fetal weight distribution in women with type I diabetes. *BJOG* 2000;107:1001-1006.

42. 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* 2003;111:9-14.

43. Mulik V, Usha Kiran TS, Bethal J, Bhal PS. The outcome of macrosomic fetuses in a low risk primigravid population. *Int J Gynaecol Obstet* 2003;80:15-22.

44. Stotland NE, Caughey AB, Breed EM, Escobar GJ. Risk factors and obstetric complications associated with macrosomia. *Int J Gynaecol Obstet* 2004;87:220-226.

Samenvatting en Conclusies

Samenvatting

Een ongecompliceerde zwangerschap met een gezond kind als uitkomst is de doelstelling van de behandeling van zwangere vrouwen met type 1 diabetes mellitus.[1] Helaas gaan de zwangerschappen van deze vrouwen nog gepaard met drie tot zesmaal zoveel perinatale complicaties ten opzichte van de gezonde populatie.[2-7] Dit is verbazingwekkend gezien het feit dat de diabetes bij het merendeel van deze vrouwen goed gereguleerd is volgens internationale richtlijnen.[8] Deze richtlijnen stellen dat het complicatierisico bij zwangere vrouwen met diabetes gelijk zou zijn aan dat van de gezonde populatie wanneer het HbA_{1c} minder dan 1% boven de bovengrens van 'normaal' is.[8] Gezien het nog steeds verhoogde complicatierisico is de veronderstelde 'veilige' HbA_{1c}-grenswaarde blijkbaar niet veilig genoeg.
De meest voor de hand liggende verklaring voor de problemen die gezien worden tijdens zwangerschappen van vrouwen met type 1 diabetes, is het regelmatig optreden van kortdurende hyperglycaemieën. Deze kortdurende hyperglycaemieën worden waarschijnlijk niet weergegeven door het HbA_{1c}, aangezien dit de glucoseregulatie over een langere periode (twee tot drie maanden) weergeeft.[9] Eerder onderzoek heeft aangetoond dat tijdens de zwangerschap de post-prandiale glucosepieken van vrouwen met type 1 diabetes uitzonderlijk hoog zijn en dat deze pieken niet geregistreerd worden bij routinecontrole.[10,11]
Een nieuw instrument voor het continu meten van glucosewaarden is het 'Continuous Glucose Monitoring System' (CGMS). Met dit systeem is het mogelijk om in de thuissituatie gedurende maximaal 72 uur iedere vijf minuten een glucosewaarde te meten in het subcutane vetweefsel. Met het beschikbaar komen van het CGMS ontstond de mogelijkheid om bij zwangere vrouwen met type 1 diabetes 24-uurs glucoseprofielen te bestuderen en om de relatie tussen deze profielen en de zwangerschapsuitkomst te bepalen.

Het CGMS meet glucosespiegels door elektrochemische detectie in het interstitiële vocht van het onderhuidse vetweefsel van de buik. Onderzoek heeft aangetoond dat glucosespiegels in het interstitiële weefsel 20 tot 50% lager zijn dan bloedglucosespiegels.[12] IJking van het CGMS met capillaire bloedglucosewaarden stelt het systeem in staat te corrigeren voor dit verschil.
Bij niet-zwangere patiënten met diabetes is echter aangetoond dat het systeem niet altijd naar tevredenheid werkt.[13-15] In *hoofdstuk 2* hebben we de nauwkeurigheid van het CGMS bij zwangere vrouwen met type 1 diabetes onderzocht. Van 15 patiënten zijn in totaal 239 capillaire bloedglucosewaarden gemeten en gerelateerd aan simultaan gemeten CGMS glucosewaarden. De correlatiecoëfficiënt van deze waarden was 0.94 ($p<0.001$). Bij 6% van de gepaarde data werd een verschil gevonden dat klinisch van belang zou kunnen zijn. In alle paren waar een verschil gezien werd wat klinische consequenties zou kunnen hebben, lag één van de waarden

onder de hypoglycaemie-grens van 3.9 mmol/l terwijl de andere een normale glucosewaarde was.
In *hoofdstuk 3* hebben we de reproduceerbaarheid van het CGMS getoetst door het vergelijken van de glucoseprofielen van twee gelijktijdig gedragen CGMS apparaten. Vijf zwangere vrouwen met type 1 diabetes hebben deelgenomen aan dit onderzoek. De correlatiecoëfficiënt van simultaan gemeten waarden was 0.94 ($p<0.001$). In bijna 80% van de gepaarde data konden beide waarden geclassificeerd worden als normoglycaemisch, hypoglycaemisch of hyperglycaemisch. In 81% van de gepaarde data die niet concordant waren, werd één waarde geclassificeerd als normoglycaemisch en één als hypoglycaemisch.
We hebben geconcludeerd dat de nauwkeurigheid en reproduceerbaarheid van het CGMS bij gebruik door zwangere vrouwen met type 1 diabetes adequaat zijn. De kleine hoeveelheid fouten die het systeem maakt, wordt voornamelijk gemaakt in het hypoglycaemische gebied hetgeen in overeenstemming is met de bevindingen bij niet-zwangere patiënten met diabetes.[15,17,18] Aangezien er geen constant verschil is tussen de glucosespiegels die gemeten zijn met gelijktijdig gedragen CGMS apparaten, lijken de fouten veroorzaakt te worden door technische (het meten van het elektrische signaal dat gecreëerd wordt door de reactie van glucose-oxidase met glucose) of analytische (het omzetten van het elektrische signaal in glucosewaarden) tekortkomingen.
Het CGMS is een apparaat dat een bijdrage kan leveren aan de behandeling van type 1 diabetes bij zwangere vrouwen. Aangezien het systeem sporadisch misleidend kan zijn, moet het beschouwd worden als een aanvullende methode voor het meten van glucosewaarden.

De definitie van normoglycaemie tijdens de zwangerschap is tot op heden niet vastgesteld. Het gebrek aan kennis omtrent de glucosehuishouding van gezonde zwangere vrouwen belemmert de behandeling van zwangere vrouwen met diabetes. In *hoofdstuk 4* worden de 24-uurs glucoseprofielen van 12 gezonde zwangere vrouwen beschreven. Deze vrouwen gebruikten het CGMS driemaal tijdens en eenmaal na de zwangerschap. Nachtelijke en nuchtere glucosespiegels daalden met het vorderen van de zwangerschap. Regelmatig werden waarden beneden de ondergrens van normoglycaemie buiten de zwangerschap (3.9 mmol/l) gemeten. Postprandiale glucosewaarden stegen gedurende de zwangerschap en overschreden regelmatig de bovengrens van normoglycaemie buiten de zwangerschap (7.8 mmol/l). De daling van nachtelijke glucosewaarden kan toegeschreven worden aan het feit dat de tweede helft van de zwangerschap beschouwd kan worden als een katabole toestand.[19] Tijdens deze fase van de zwangerschap worden de glycogeenvoorraden in de lever aangesproken. Dit heeft een verhoogde gluconeogenese tot gevolg wanneer de vrouwen rusten.[20] De verhoogde gluconeogenese kan, gecombineerd met een verhoogd glucoseverbruik, leiden tot hypoglycaemie. Deze hypoglycaemieën zijn het meest evident na een langere periode van vasten, zoals de nacht.[21,22]

De stijging van post-prandiale glucosewaarden is het gevolg van een daling van de insulinegevoeligheid van perifere weefsels in het derde trimester van de zwangerschap.[23-25] Dit leidt tot een verminderde glucosetolerantie aan het einde van de zwangerschap. De gedachte is dat de verhoogde glucosewaarden nodig zijn om het glucoseverbruik van de groeiende foetus te compenseren.[26,27]
Onze bevindingen kunnen een bijdrage leveren aan het vaststellen van het doel van de behandeling van zwangere vrouwen met type 1 diabetes. De behandeling van deze vrouwen dient gericht te zijn op het voorkomen van hyperglycaemieën. Sporadische post-prandiale overschrijding van de hyperglycaemie-grens is aanvaardbaar aangezien dit een normaal verschijnsel (tot 10.0 mmol/l) blijkt te zijn bij gezonde zwangere vrouwen. Helaas gaat het aanscherpen van de glucoseregulatie gepaard met een toegenomen kans op hypoglycaemieën.[28] Dit risico is waarschijnlijk het hoogst in de nacht wanneer lage glucosewaarden ook voorkomen bij gezonde zwangere vrouwen. De behandeling van zwangere vrouwen met diabetes moet daarom gericht zijn op het vinden van een balans tussen de strakheid van de glucoseregulatie en de kans op hypoglycaemieën.

Volgens de American Diabetes Association zijn HbA_{1c}-waarden binnen 1% boven 'normaal' (m.a.w. 6.0-7.0%) 'veilig' tijdens de zwangerschap. Populatiestudies laten echter zien dat er nog steeds verhoogde aantallen complicaties zijn bij vrouwen met 'veilige' HbA_{1c}-waarden.[6] In *hoofdstuk 5* hebben we de glucoseprofielen van zwangere vrouwen met type 1 diabetes in het eerste trimester van de zwangerschap vergeleken met hun HbA_{1c}-waarden. CGMS glucoseprofielen werden verkregen van 13 vrouwen met een zwangerschapsduur tussen 7 en 15 weken. Negen patiënten hadden een $HbA_{1c} \leq 7.0\%$ terwijl 41% van de metingen een glucosewaarde ≤ 3.9 mmol/l en 53% van de metingen een glucosewaarde ≥ 7.8 mmol/l weergaf. Ten eerste laten deze bevindingen zien dat HbA_{1c}-waarden geen adequate weergave zijn van de complexiteit van glucoseprofielen bij zwangere vrouwen met type 1 diabetes. Ten tweede wijzen deze resultaten erop dat patiënten pas scherp zijn ingesteld wanneer het HbA_{1c} echt 'normaal' is (4.0-6.0%).
In *hoofdstuk 6* worden de HbA_{1c}-grenswaarden zoals die momenteel gebruikt worden in internationale richtlijnen, verder geëxploreerd door het relateren van de glucoseprofielen van 185 CGMS meetdagen van 43 vrouwen met hun HbA_{1c}-waarden. De glucoseprofielen werden vergeleken tussen vrouwen met een 'normaal' HbA_{1c}, een 'veilig' HbA_{1c} en een 'verhoogd' HbA_{1c} (>7.0%). De glucoseprofielen van vrouwen met een 'normaal' HbA_{1c} waren significant beter dan die van vrouwen met een 'veilig' of een 'verhoogd' HbA_{1c}. Er was geen verschil tussen de glucoseprofielen van vrouwen met een 'veilig' of een 'verhoogd' HbA_{1c}. Deze bevindingen geven wederom aan dat de behandeling van diabetes bij zwangere vrouwen gericht moet zijn op het bereiken van normale HbA_{1c}-waarden.
Voor de behandeling van diabetes is het regelmatig zelf meten van capillaire bloedglucosewaarden (SMBG) van groot belang.[29-32] Een minimum van drie

SMBG per dag wordt aanbevolen tijdens de zwangerschap van vrouwen met diabetes.[33] Om te bepalen welk aantal SMBG per dag nodig is om een reëel beeld te krijgen van het dagelijkse glucoseprofiel, hebben we de glucoseprofielen die gemeten zijn door middel van SMBG en met het CGMS vergeleken tussen vrouwen met 4-5, 6-9 en ≥10 SMBG per dag. De detectie van hyperglycaemische episodes is 100% wanneer vrouwen zich minimaal 10 keer per dag meten. De detectie van hypoglycaemische episodes verbetert significant wanneer vrouwen zich minimaal 10 maal per dag meten maar is maximaal 73%. Het is onwaarschijnlijk dat de detectie van hypoglycaemieën 100% wordt, aangezien veel hypoglycaemische episodes 's nachts plaatsvinden terwijl de vrouwen slapen.[34,35]
Kortom, bijna 'normale' HbA_{1c}-waarden zijn niet goed genoeg. 'Veilige' glucoseregulatie zou gedefinieërd moeten worden als normoglycaemie. Als men echter de verhoogde kans op ernstige hypoglycaemieën in gedachten neemt die gepaard gaat met het strak instellen van de diabetes, kan normoglycaemie niet altijd als 'veilig' voor de moeder beschouwd worden.[28,34,36,37] Om de optimale balans te kunnen vinden tussen scherpe diabetesinstelling en de kans op hypoglycaemieën, is nauwkeurige kennis van het dagelijkse glucoseprofiel noodzakelijk. Om dit te bereiken moeten vrouwen zich minimaal 10 maal per dag meten. Wij realiseren ons dat dit in de praktijk niet altijd haalbaar zal zijn.

Om normoglycaemie te bereiken, is het nauwkeurig afstellen van insulineschema's noodzakelijk. Het afstellen van insulineschema's op basis van regelmatige SMBG of CGMS metingen is alleen haalbaar wanneer de verschillen tussen de glucoseprofielen op opeenvolgende dagen (dag-tot-dag variabiliteit) klein zijn. In *hoofdstuk* 7 hebben we de glucose dag-tot-dag variabiliteit van zwangere vrouwen met type 1 diabetes bestudeerd. We hebben tevens gekeken naar de effecten van deze variabiliteit op de behandeling. Eénendertig zwangere vrouwen met diabetes hebben het CGMS twee opeenvolgende dagen gebruikt. Op basis van visuele inspectie van de tweedaagse glucoseprofielen, werd 55% van de vrouwen geclassificeerd als hebbende lage dag-tot-dag variabiliteit (Mean Absolute Difference 0.92-2.33 mmol/l) en werd 45% geclassificeerd als hebbende hoge dag-tot-dag variabiliteit (MAD 2.41-6.12 mmol/l). Er is geen invloed gevonden van maternale leeftijd en BMI, duur van de diabetes, White-classificatie, aantal SMBG en aantal insuline injecties per dag, zwangerschapsduur, voeding, lichaamsbeweging, het samenwonen met kinderen en methode van insulinetoediening op het optreden van lage of hoge dag-tot-dag variabiliteit. Vrouwen met hoge dag-tot-dag variabiliteit hebben significant hogere schommelingen gedurende de dag en hogere HbA_{1c}-waarden dan vrouwen met lage dag-tot-dag variabiliteit. Het verschil in behandeladvies op basis van de glucoseprofielen van dag 1 of dag 2 van de CGMS meting was significant hoger in de groep vrouwen met hoge dag-tot-dag variabiliteit ($p<0.01$) vergeleken met de groep vrouwen met lage dag-tot-dag variabiliteit. Dit betekent dat het aanpassen van insulineschema's bij ongeveer de helft van de vrouwen belemmerd

wordt door hoge dag-tot-dag variabiliteit.
In *hoofdstuk 8* is bepaald wat de meerwaarde is van driedaagse ten opzichte van tweedaagse CGMS metingen. De evaluatie van 36 driedaagse CGMS metingen liet zien dat in 88% van de vrouwen met lage dag-tot-dag variabiliteit tussen dag 1 en dag 2 van de meting, het glucoseprofiel van dag 3 niet verschilde van dat van dag 2. Een tweedaagse CGMS meting lijkt daarom voldoende om vrouwen met lage dag-tot-dag variabiliteit te identificeren. Bij de vrouwen met een hoge dag-tot-dag variabiliteit tussen dag 1 en dag 2 van de meting, had 79% ook een hoge variabiliteit tussen dag 2 en dag 3 van de meting. Bij deze vrouwen kan de CGMS meting gebruikt worden voor het verhogen van het inzicht in de glucoseregulatie en zal dat hopelijk leiden tot aanpassingen in het eetgedrag en de leefgewoonten. Technisch bleek het niet altijd mogelijk om drie onafgebroken opeenvolgende meetdagen te verkrijgen (in slechts 36 uit 100 metingen van 47 vrouwen).
Dag-tot-dag variabiliteit is een probleem bij de behandeling van zwangere vrouwen met diabetes en verder onderzoek naar verklarende factoren zoals stress, diabetische neuropathie en eetgewoonten dient verricht te worden. Tweedaagse metingen zijn over het algemeen voldoende om te kunnen differentiëren tussen vrouwen met lage en hoge dag-tot-dag variabiliteit. Ongeveer de helft van de zwangere vrouwen met type 1 diabetes heeft lage dag-tot-dag variabiliteit. Aanpassingen in insulineschema's op basis van de CGMS meting kunnen veilig gedaan worden bij deze vrouwen.

De meest voorkomende complicatie geassocieerd met zwangerschappen van vrouwen met diabetes is macrosomie van het kind (geboortegewicht $\geq 90^{ste}$ percentiel).[3,6,7,38] In de gezonde populatie is aangetoond dat de correlatie tussen geboortegewicht van broers en/of zussen sterk is. De voorspellende waarde van het geboortegewicht van een eerder geborene op het geboortegewicht van later geborenen ligt tussen de 20 en 30%.[39,40] Bij vrouwen met type 1 diabetes is de voorspellende waarde van het HbA_{1c} op het geboortegewicht van hun kinderen niet meer dan 10%.[7,41] In *hoofdstuk 9* worden de voorspellende waarde van het geboortegewicht van eerder geborenen en van het gemiddelde HbA_{1c} van de moeder tijdens de zwangerschap op het geboortegewicht van kinderen van vrouwen met type 1 diabetes onderzocht. Analyse van 214 zwangerschappen van 107 vrouwen met type 1 diabetes laat zien dat het geboortegewicht van een tweede kind significant gerelateerd is aan het geboortegewicht van een eerder geboren kind. Veertig tot vijftig procent van de variantie in geboortegewicht van tweede kinderen kan verklaard worden door het geboortegewicht van het eerste kind. Vijfentachtig procent van de vrouwen die een extreem macrosoom kind (geboortegewicht $\geq 97.7^{ste}$ percentiel) kregen, zette bij de volgende zwangerschap opnieuw een extreem macrosoom kind op de wereld. Er werd geen significante correlatie gevonden tussen gemiddeld HbA_{1c} en geboortegewicht.
Bij vrouwen met type 1 diabetes zou het geboortegewicht van eerdere kinderen en niet het HbA_{1c} gebruikt moeten worden voor het identificeren van patiënten met

een verhoogd risico op het krijgen van een macrosoom kind. Het baren van een macrosoom kind gaat gepaard met een verhoogde kans op een scala aan complicaties: langdurige partus, kunstverlossingen, schouderdystocie, sectio caesaria, Apgar score <4 en opname van het kind op de kinderafdeling.[42-44] Het tijdig identificeren van patiënten met een verhoogd risico op deze complicaties met als gevolg het afstemmen van de glucoseregulatie en de obstetrische behandeling op de individuele behoeften van de patiënt, is daarom van groot belang.

Tot dusver hebben we aangetoond dat de relatie tussen het HbA_{1c} en het geboortegewicht van kinderen van vrouwen met diabetes zwak is en dat het HbA_{1c} geen goede weergave is van de complexiteit van de glucosehuishouding bij deze vrouwen. De volgende stap was het bepalen van de relatie tussen glucoseprofielen en het geboortegewicht van het kind. In *hoofdstuk 10* laten we zien dat het 24-uurs glucoseprofiel van vrouwen met diabetes die een macrosoom kind baren anders is dan dat van vrouwen met diabetes die een kind met een normaal geboortegewicht op de wereld zetten. Vijftig zwangere vrouwen met type 1 diabetes en 12 gezonde zwangere vrouwen (zie *hoofdstuk 4*) hebben ieder trimester van hun zwangerschap eenmaal het CGMS gebruikt. Zonder uitzondering hadden de vrouwen met diabetes hogere glucosewaarden dan de gezonde zwangere vrouwen. Zestig procent van de vrouwen met diabetes kreeg een macrosoom kind. Van deze kinderen was 40% 'vroeg macrosoom' (groeiparameters $\geq 95^{ste}$ percentiel bij echografische controle bij een zwangerschapsduur ≤ 30 weken). Al deze kinderen waren extreem macrosoom bij geboorte. Slechts 21% van de kinderen met 'late macrosomie' (verhoogde groeiparameters bij echografische controle >30 weken) was extreem macrosoom bij de geboorte. Alle vrouwen die een vroeg macrosoom kind kregen, hadden in het tweede trimester gedurende een groot gedeelte van de dag verhoogde glucosewaarden. De vrouwen die een laat macrosoom kind of een kind met een normaal geboortegewicht kregen, hadden in dit trimester normale glucosewaarden. In het derde trimester hadden de vrouwen die een macrosoom kind kregen allen significant hogere schommelingen gedurende de dag vergeleken met de vrouwen met diabetes die een kind met een normaal gewicht kregen. Alleen in het derde trimester van de zwangerschap waren de HbA_{1c}-waarden significant gerelateerd aan het geboortegewicht van het kind ($r=0.554$, $p<0.01$). Bij alle vrouwen met diabetes was de mediane HbA_{1c}-waarde niet hoger dan 7.0% en dus 'veilig'.
Verhoogde glucosewaarden en glucoseschommelingen spelen dus beide een rol bij het ontstaan van macrosomie bij kinderen van vrouwen met type 1 diabetes. Vrouwen die het risico lopen een macrosoom kind te krijgen kunnen worden geïdentificeerd door verhoogde glucosewaarden in het tweede trimester van de zwangerschap. Intensieve controle van glucosewaarden en insuline-aanpassingen bij verhoogde waarden zijn daarom met name belangrijk in het tweede trimester van de zwangerschap als men excessieve groei van de foetus en de daaraan verbonden complicaties wil voorkomen.[42-44]

Conclusies

Het 'Continuous Glucose Monitoring System' (CGMS) kan een bijdrage leveren aan de behandeling van type 1 diabetes bij zwangere vrouwen. Het gebruik van het CGMS tijdens de zwangerschap verhoogt het inzicht in de glucoseregulatie wat kan leiden tot aanpassingen in eetgedrag en leefgewoonten. Als de schommelingen in de glucoseprofielen op opeenvolgende dagen klein zijn, kan het systeem ook gebruikt worden voor aanpassingen in insulineschema's.

Glucosewaarden onder de hypoglycaemie-grens, met name 's nachts, en sporadische post-prandiale overschrijdingen van de hyperglycaemie-grens (tot 10.0 mmol/l) zijn normaal tijdens de zwangerschap van gezonde vrouwen.

HbA_{1c}-waarden van zwangere vrouwen met type 1 diabetes geven niet de complexiteit weer van de dagelijkse glucoseprofielen. Bij deze vrouwen dient gestreefd te worden naar normale HbA_{1c}-waarden. De behandeling van zwangere vrouwen met type 1 diabetes dient gericht te zijn op het vinden van een balans tussen de strakheid van de glucoseregulatie en de kans op hypoglycaemieën.

De behandeling van zwangere vrouwen met type 1 diabetes dient gebaseerd te zijn op een nauwkeurige weergave van de dagelijkse glucoseprofielen. De meest nauwkeurige weergave wordt verkregen door het regelmatig zelf meten, minimaal tien maal per dag, van capillaire bloedglucosewaarden.

Grote verschillen tussen de glucoseprofielen op opeenvolgende dagen is een probleem bij de behandeling van zwangere vrouwen met type 1 diabetes. Deze verschillen belemmeren de afstelling van insulineschema's. Dit komt bij de helft van de zwangere vrouwen met type 1 diabetes voor.

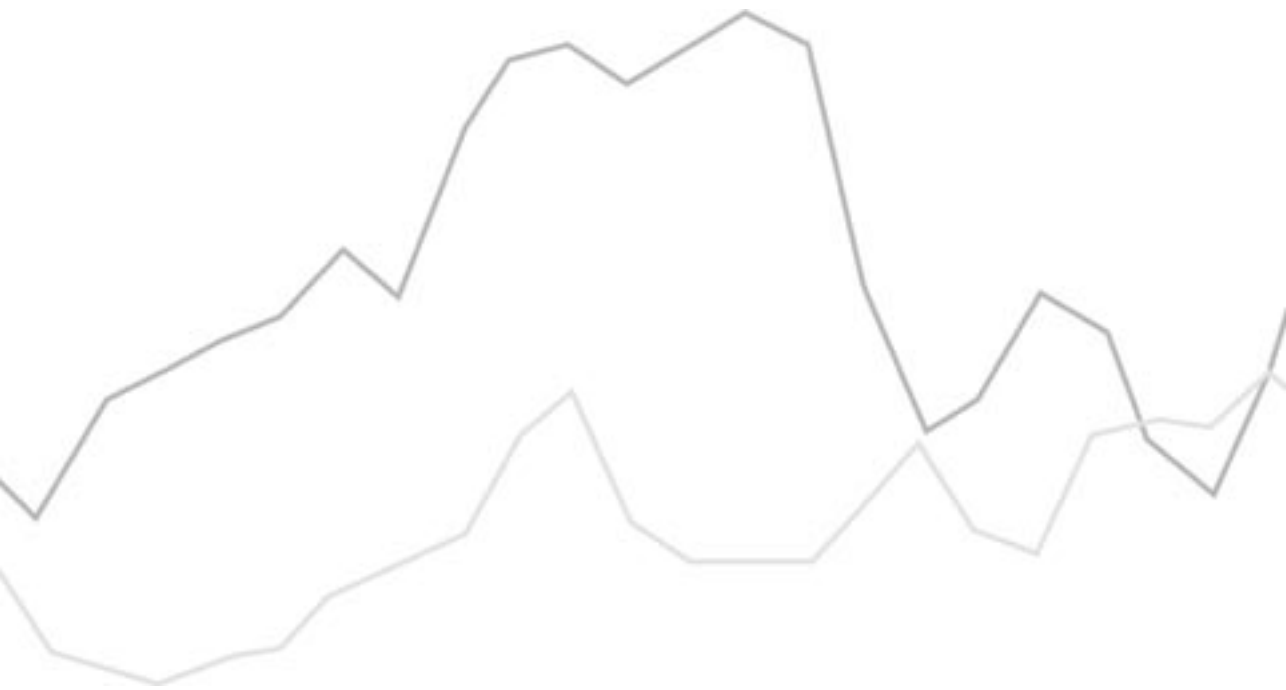
Het geboortegewicht van eerdere kinderen is een betere voorspeller voor het optreden van macrosomie dan het HbA_{1c}.

Vrouwen met type 1 diabetes die een extreem macrosoom kind krijgen, hadden verhoogde glucosewaarden in het tweede trimester van de zwangerschap en verhoogde glucosevariabiliteit in het derde trimester van de zwangerschap. Om excessieve groei van de foetus te voorkomen is strakke regulatie van de diabetes tijdens de zwangerschap, en dan vooral tijdens het tweede trimester, van groot belang.

Referenties

Zie Summary and Conclusions, pagina 129.

Dankwoord



Dankwoord

Allereerst wil ik alle proefpersonen bedanken die hebben deelgenomen aan mijn onderzoek. Zonder de gemotiveerde bijdrage van deze vrouwen was het niet mogelijk geweest dit project tot een goed einde te brengen.

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De leden van de beoordelingscommissie prof. dr. I.M. Hoepelman, prof. dr. H.W Bruinse, prof. dr. G.E.H.M. Rutten, dr. L.L.H. Peeters en dr. E. van Ballegooie wil ik bedanken voor het kritisch doorlezen van dit proefschrift.

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Mijn paranimfen Ayten Elvan en Leonoor van der Wal
Lieve Ayten, als kamergenoten hebben wij veel met elkaar gedeeld. Ik ben blij dat jij, terwijl je zelf midden in de afronding van je eigen proefschrift zit, ook deze dag met mij wilt delen.
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Lieve Jet, jouw komst zette mijn wereld op zijn kop en je liet mij zien wat belangrijk is in het leven. Jij staat, samen met papa, met stip op nummer 1.

List of publications

Poor glucose control in women with type 1 diabetes mellitus and 'safe' HbA_{1c}-values in the first trimester of pregnancy.
A. Kerssen, I.M. Evers, H.W. de Valk, G.H.A. Visser
J Matern Fetal Neonat Med 2003; 13: 309-313.

Day-to-day glucose variability in pregnancy complicated by type 1 diabetes mellitus: glucose profiles measured with the Continuous Glucose Monitoring System.
A. Kerssen, H.W. de Valk, G.H.A. Visser
BJOG 2004; 111: 919-924.

The Continuous Glucose Monitoring System during pregnancy; accuracy assessment.
A. Kerssen, H.W. de Valk, G.H.A. Visser
Diabetes Technol Ther 2004; 6: 645-651.

Effect of breast milk of diabetic mothers on bodyweight of the offspring in the first year of life.
A. Kerssen, I.M. Evers, H.W. de Valk, G.H.A. Visser
Eur J Clin Nutr 2004; 58: 1429-31.

Diabetes en zwangerschap; het voorkómen van hypoglykemie.
G.H.A. Visser, I.M. Evers, A. Kerssen, H.W. de Valk
Ned Tijdschr Geneeskd 2005; 149: 172-6.

Curriculum Vitae

Anneloes Kerssen werd op 5 november 1974 geboren te Nuenen. In 1993 behaalde zij haar V.W.O. diploma aan het Eckart College in Eindhoven. In datzelfde jaar begon zij aan de studie Geneeskunde aan de Universiteit Utrecht. In de doctoraal fase van deze studie maakte zij voor het eerst kennis met het opzetten en uitvoeren van wetenschappelijk onderzoek. Na een keuze co-schap oncologische gynaecologie in het UMC Utrecht besloot zij verder te gaan in de Gynaecologie & Obstetrie. Na het behalen van haar artsexamen in 2001 startte zij als AGNIO Gynaecologie & Obstetrie in het UMC Utrecht. Na ruim 10 maanden als AGNIO gewerkt te hebben, begon zij onder leiding van prof. dr. G.H.A. Visser aan het promotieonderzoek dat heeft geresulteerd in dit proefschrift.
Het vele intensieve patiëntencontact tijdens haar onderzoek was een aspect waar zij zeer van genoot en heeft haar doen inzien dat een vak waar de psychosociale begeleiding van patiënten een grotere rol speelt, beter bij haar past. Zij zal daarom na afronding van haar promotieonderzoek starten met de opleiding huisartsgeneeskunde.
Anneloes Kerssen woont samen met Ruben Witlox en zij hebben een dochter Jet.