Changes in the Glycemic Profiles of Women With Type 1 and Type 2 Diabetes During Pregnancy

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OBJECTIVE — To examine the changes in glycemic excursions that occur during pregnancy using continuous glucose monitoring and to compare patterns of glycemia in pregnant women with type 1 and type 2 diabetes.

RESEARCH DESIGN AND METHODS — An observational data analysis was performed from a prospective randomized study of continuous glucose monitoring in 57 women with pregestational type 1 ($n = 40$) or type 2 ($n = 17$) diabetes with 7-day continuous glucose monitoring system profiles during each trimester. Serial glucose measurements were divided into periods of euglycemia (70–140 mg/dl), hyperglycemia (>140 mg/dl), and hypoglycemia (<70 mg/dl). Generalized linear mixed effects models were fitted to the repeated measures data to determine how these glycemic characteristics varied during gestation and by diabetes type.

RESULTS — A total of 180 continuous glucose profiles were examined (140 type 1 diabetes, 40 type 2 diabetes), providing 20,433 h of data for analysis (16,117 h type 1 diabetes, 4,316 type 2 diabetes). Women with type 2 diabetes spend ~33% less time hyperglycemic throughout pregnancy than women with type 1 diabetes ($P = 0.005$), with a significantly more rapid reduction in time spent hyperglycemic in early pregnancy ($P = 0.02$). Although women with type 2 diabetes spend less overall time hypoglycemic ($P = 0.04$), their risk of nocturnal hypoglycemia is equivalent to that of women with type 1 diabetes (blood glucose level <70 mg/dl, $P = 0.9$; blood glucose level <50 mg/dl, $P = 0.2$).

CONCLUSIONS — Continuous glucose monitoring reveals clear differences in the level of glycemic control that exist in women with type 1 and type 2 diabetes. These data will guide therapeutic interventions aimed at optimizing glycemic control and improving the pregnancy outcomes of both type 1 and type 2 diabetes.

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Recent nationwide studies from both the U.K. and the Netherlands confirm that the outcomes of pregnancy for women with diabetes remain poor, with increased rates of congenital malformation, perinatal mortality, premature delivery, and macrosomia (1,2). It has also been shown that the outcomes of pregnancy in women with type 2 diabetes are at least as poor as for women with type 1 diabetes (1,3–8). Some studies, including our own regional audit, suggest that women with type 2 diabetes, who are older, more obese, and more likely to belong to an ethnic minority group, may have even poorer pregnancy outcomes than women with type 1 diabetes (5–7,9). With the increasing prevalence of obesity in developed countries, type 2 diabetes has become the most common form of diabetes in women of reproductive age (10,11), accounting for one-third to one-half of all diabetic pregnancies (12). Yet compared with pregnancies complicated by type 1 diabetes, very little is known about blood glucose control during pregnancy for women with type 2 diabetes. The published series suggest minimal differences in overall measures of glycemia, with a possible small decrease in A1C for women with type 2 diabetes during the second trimester (6,12).

Continuous glucose monitoring systems (CGMSs) provide greater insight into glucose levels throughout the day, yielding information on the magnitude, frequency, and duration of glucose excursions not available with conventional glucose self-monitoring. The importance of CGMS data are well recognized, described as a "stepping stone in the journey toward a cure" and "a roadmap for effective diabetes management" (13,14). The slow kinetics of glycosylated hemoglobin accumulation and physiological changes in erythrocyte formation during pregnancy mean that A1C is only a limited predictor of acute blood glucose changes (15,16), providing an explanation for the poor pregnancy outcomes, even in women with apparently "good" glycemic control (2,17,18). Recent attention has therefore focused on evaluating the role of CGMS in pregnancy with studies providing normative data in nondiabetic pregnancies (19) and highlighting the prevalence of glycemic excursions during early pregnancy in women with type 1 diabetes (18,20–23).

Because CGMS is still a relatively new tool and remains expensive for routine clinical use, there is a paucity of longitudinal data throughout pregnancy, even for women with type 1 diabetes. Furthermore, despite their poor pregnancy outcomes, there are no continuously monitored data detailing the glycemic characteristics of women with type 2 diabetes. This study using 7-day CGMS profiles provides serial data regarding the glycemic profiles of women with both

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Abbreviations: CGMS, continuous glucose monitoring system.

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

type 1 and type 2 diabetes. The objectives were first to examine changes in the daily patterns of glucose excursions with increasing gestation and second to compare differences between women with type 1 and type 2 diabetes.

RESEARCH DESIGN AND METHODS

— A prospective randomized study comparing CGMS to conventional blood glucose monitoring in pregnancies complicated by pregestational diabetes was undertaken at two specialist diabetic antenatal clinics in the U.K. from September 2003 to 2006. Here, we have analyzed the profiles collected during the study to evaluate the changes in glycemic profiles over gestation and the differences between type 1 and type 2 diabetes in pregnancy. Appropriate research governance and ethics committee approval was obtained at both sites. Women with documented pregestational type 1 and type 2 diabetes were enrolled if they had a confirmed positive pregnancy test and ultrasound dating scan, were between 16 and 45 years of age, provided written informed consent, and were willing to wear the CGMS device for up to 7 days during each trimester. Women randomized to the CGMS intervention were encouraged to wear the device at 4- to 6-week intervals from the booking visit through to 34 weeks' gestation, since our clinical experience suggests greater discomfort associated with wearing the device in later pregnancy. The prepregnancy and antenatal care at these centers has been recently documented (24).

Of the 79 consecutive women with pregestational diabetes approached, 57 women agreed to participate (72%), were trained in the use of the CGMS, and had sensors implanted into the upper outer buttock, alternating between sides, by research nurses at antenatal diabetes clinics. Subjects continued their usual finger-stick blood glucose monitoring with at least seven measurements per day, aiming for fasting blood glucose <95 mg/dl, 130–140 mg/dl 1 h after meals, and <120 mg/dl 2 h after meals. The data were downloaded to a personal computer using the software (Medtronic Comstation, version 1.7B) provided by the manufacturer after 1 week and shared with women and their health care team. Therapeutic adjustments were made by the usual combined obstetric/diabetes team, based on both finger-stick and continuous data. Women were managed with short-acting insulin analogs before meals and with once- or twice-daily intermediate-acting insulin, long-acting insulin analogs, or insulin pump therapy if started before pregnancy. All women with type 2 diabetes were started on insulin before pregnancy or as soon as pregnancy was confirmed if they had not attended for prepregnancy care.

Study population

Of the participating women, 40 of 57 (70%) had type 1 diabetes and 17 of 57 (30%) had type 2 diabetes. The mean age of the entire study group was 31.5 ± 7.1 years (31.1 ± 6.1 years for type 1 vs. 32.7 ± 9.1 years for type 2; $P = 0.4$), with 70% of women having planned their pregnancies (73% type 1, 65% type 2; $P = 0.6$). Women with type 1 diabetes had a longer duration since diagnosis (18.5 ± 9.3 vs. 5.8 ± 7.1 years; $P < 0.0001$) and were less obese at the booking visit (mean BMI 25.5 ± 4.5 vs. 38.0 ± 10.7 kg/m^2; $P = 0.0001$) than women with type 2 diabetes. There was no significant difference between A1C at booking between women with type 1 and type 2 diabetes (7.2 ± 1.7 and 7.0 ± 1.1%, respectively; $P = 0.6$).

There were no statistically significant differences between the 57 subjects who participated in the study and those who declined to participate ($n = 22$) in mean age, duration of diabetes, ethnicity, type of diabetes, uptake of prepregnancy counseling, or parity. This suggests the patients studied were representative of women with diabetes attending our antenatal clinics.

Study device

The CGMS device (CGMS Gold Medtronic; MiniMed, Northridge, CA) consists of a disposable subcutaneous glucose-sensing device and a glucose oxidase–impregnated electrode connected by a cable to a lightweight monitor. Interstitial glucose values in subcutaneous tissues, within a range of 40–400 mg/dl, are measured electrochemically every 10 s, and an average value is stored in the monitor every 5 min, providing up to 288 blood glucose measurements per day. The subjects are unaware of the results of the sensor measurements during monitoring. The system is recalibrated each time a blood glucose measurement is entered into the device, and subjects are asked to do this at least four times per day. The accuracy, reliability, and measurement of glycemic control by CGMS has been confirmed with sensor modification, allowing the device to be worn for up to 7 days (25,26).

Statistical analysis

Serial glucose measurements for all subjects were analyzed using summary measures to characterize each subject's glucose profile. Each profile was divided into periods of euglycemia (70–140 mg/dl), hypoglycemia (<70 mg/dl), and hyperglycemia (>140 mg/dl). Extreme hypoglycemic excursions were defined as <50 mg/dl and extreme hyperglycemic excursions as >200 mg/dl. An excursion into either the hypoglycemic or hyperglycemic range required a duration of at least 30 min per definitive episode.

For each subject, the proportions of time spent euglycemic, hyperglycemic, and hypoglycemic were determined from the continuously monitored data. The total area under the curve for each glucose threshold was determined, representing both the duration and magnitude of the glucose excursions. Mean blood glucose values from the CGMS data and A1C measurements taken at 4-week intervals, assayed using the Diabetes Control and Complications Trial–aligned Biomen 8140 method (normal reference range 3.6–5.8%), were calculated for each trimester, with the first trimester defined as up to 13 weeks' gestation, second trimester 13–28 weeks' gestation, and third trimester from 28 weeks' gestation onward.

To provide statistical comparisons for and estimates of the summary measures for type 1 and type 2 diabetes at different stages of gestation, generalized linear mixed effects models were fitted to the repeated measures data (27). The main hypotheses to be tested were whether each summary measure showed differences between type 1 and type 2 diabetes, whether it changed over gestation, and whether the rate of change differed between type 1 and type 2 diabetes (time × diabetes interaction). Normally distributed random effects were fitted to the inter-individual differences in change over gestation (slope) and starting point (intercept). Within-patient correlation over time was fitted using a continuous autoregressive function. A Poisson family model with the canonical log link function was used for the amount of time spent in euglycemia, hyperglycemia, or hypoglycemia and the number of such episodes, with the total length of recorded time taken as the offset. Because area under the curve is always ≥0 (and often = 0), a log link function was used for this response

Table 1—*Estimates of glycemic characteristics at the end of each trimester for type 1 and type 2 diabetes, obtained from generalized linear mixed effects models*

Glycemic measure	Trimester 1	Trimester 2	Trimester 3	*P*
Euglycemia				
Percentage of time 70–140 mg/dl (hours per 24 h)				
Type 1	43.2% (10.4 h)	49.3% (11.8 h)	56.3% (13.5 h)	Diabetes type: 0.0001
Type 2	57.6% (13.8 h)	65.8% (15.8 h)	75.1% (18.0 h)	Gestational period: 0.0001
Hyperglycemia				
Percentage of time >140 mg/dl (hours per 24 h)				
Type 1	40.5% (9.7 h)	36.4% (8.7 h)	32.7% (7.8 h)	Diabetes type: 0.005
Type 2	32.8% (7.9 h)	19.5% (4.7 h)	11.6% (2.8 h)	Gestational period: 0.007
Area under the curve >140 mg/dl				
Type 1	23.04	17.28	12.78	Diabetes type: 0.001
Type 2	14.04	5.76	2.52	Gestational period: 0.0002
Percentage of time >200 mg/dl (hours per 24 h)				
Type 1	16% (3.8 h)	11.8% (2.8 h)	8.7% (2.0 h)	Diabetes type: 0.0004
Type 2	7.9% (1.9 h)	2.9% (0.7 h)	1.0% (0.2 h)	Gestational period: 0.0006
Hypoglycemia				
Percentage of time <70 mg/dl (hours per time period)				
Overall (24 h)				
Type 1	14.6% (3.5 h)	13.7% (3.3 h)	12.9% (3.0 h)	Diabetes type: 0.04
Type 2	10.2% (2.4 h)	9.6% (2.3 h)	9.1% (2.2 h)	Gestational period: NS
Nocturnal (2200–0600 h)				
Type 1	14.6% (1.1 h)	16.2% (1.3 h)	18.1% (1.5 h)	Diabetes type: NS
Type 2	14.8% (1.1 h)	16.5% (1.3 h)	18.4% (1.5 h)	Gestational period: NS
Area under the curve <70 mg/dl				
Type 1	2.52	2.16	1.80	Diabetes type: 0.02
Type 2	1.44	1.26	1.08	Gestational period: NS
Percentage of time <50 mg/dl (hours per time period)				
Overall (24 h)				
Type 1	5.7% (1.4 h)	4.6% (1.1 h)	3.7% (0.9 h)	Diabetes type: 0.02
Type 2	3.0% (0.7 h)	2.5% (0.6 h)	2.0% (0.5 h)	Gestational period: NS
Nocturnal (2200–0600 h)				
Type 1	7.3% (0.6 h)	6.3% (0.5 h)	5.4% (0.4 h)	Diabetes type: NS
Type 2	5.1% (0.4 h)	4.4% (0.3 h)	3.8% (0.3 h)	Gestational period: NS
Mean blood glucose (mg/dl)				
Type 1	137	128	119	Diabetes type: 0.08
Type 2	126	117	106	Gestational period: 0.009
A1C (%)				
Type 1	6.84	6.37	5.90	Diabetes type: NS
Type 2	6.56	6.09	5.62	Gestational period: 0.004

variable as well, without an offset. For A1C and mean blood glucose models, simple linear mixed effects models were used. These comprehensive models were fitted using a restricted penalized quasi-likelihood algorithm in S-plus v7.0 (Insightful, Seattle, WA).

RESULTS — During the study, 40 women with type 1 diabetes (70%) and 17 women with type 2 diabetes (30%) had a total of 180 CGMS profiles (140 type 1 diabetes, 40 type 2 diabetes). There were 40 CGMS profiles obtained during the first trimester (30 type 1 diabetes, 10 type 2 diabetes; 14 ≤8 weeks, 26 ≤12 weeks), 90 in the second trimester (69 type 1 diabetes, 21 type 2 diabetes; 28 ≤16 weeks, 24 ≤20 weeks, 26 ≤24 weeks, 12 <28 weeks), and 50 in the third trimester (41 type 1 diabetes, 9 type 2 diabetes; 24 ≤32 weeks, 19 ≤36 weeks, 7 >36 weeks). Overall 20,433 h of continuously monitored data (16,117 type 1 diabetes, 4,316 type 2 diabetes) were obtained.

To analyze the data, we extracted summary measures from each CGMS trace and fitted generalized linear mixed effects models to analyze the differences between type 1 and type 2 diabetes in these measures over the three trimesters of pregnancy. This is the most accurate approach to model multiple profiles from individual women, taken at varying gestational ages throughout pregnancy, and is a well-established technique for analyzing longitudinal data (27). In particular, we explicitly modeled and compensated for the differing number of traces downloaded for each subject and the varying gestational ages at which traces were obtained, the correlation between serial measurements in time within a given subject, and the inter-individual differences in both the starting point for glycemic control and its change during pregnancy. Table 1 provides values estimated from the models for the total proportion of time spent euglycemic, hyperglycemic, and hypoglycemic, as well as the area under

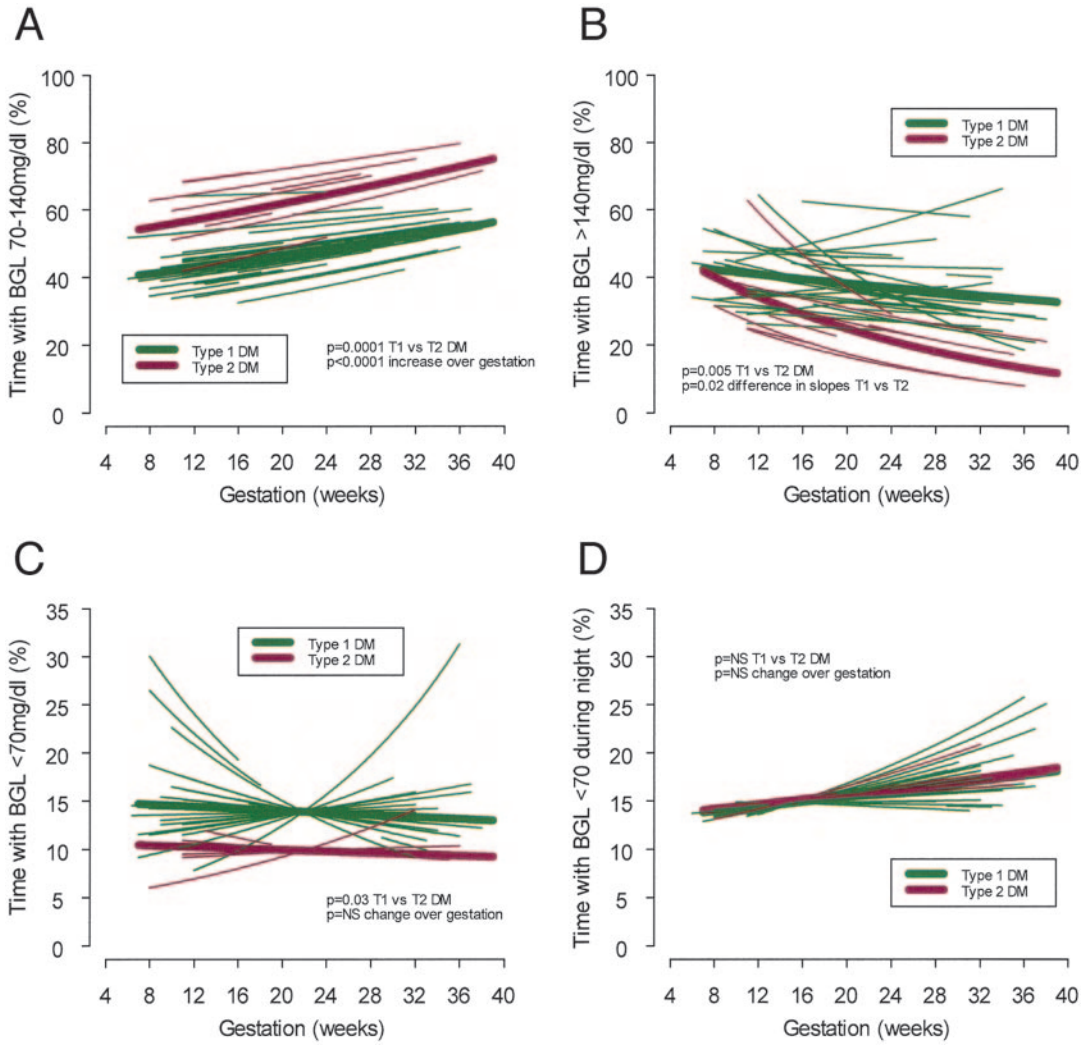

Figure 1— *Estimates of glycemic characteristics for women with type 1 (T1) and type 2 (T2) diabetes (DM) obtained from applying generalized linear mixed effects models to the intermittent 7-day continuous glucose profiles. Changes in the overall proportion of time spent euglycemic (70–140 mg/dl)* (A)*, hyperglycemic (>140 mg/dl)* (B)*, hypoglycemic (<70 mg/dl)* (C)*, and hypoglycemia overnight* (D) *during pregnancy are shown for women with type 1 diabetes (green) and type 2 diabetes (red). The thick lines represent the mean changes in duration of time spent at each threshold, whereas the thin lines reflect changes across gestation for individual subjects. BGL, blood glucose level.*

the curves, per trimester for both types of diabetes.

Euglycemia

The duration of time spent within the euglycemic range for pregnancy increased with each week of advancing gestation for women with both types of diabetes (Fig. 1*A*). The proportion of time in the euglycemic range rose from an average of 43% at the end of the first trimester to 56% at the end of the third trimester for type 1 diabetes and from 58 to 75% for women with type 2 diabetes ($P < 0.0001$ for the change over pregnancy). Women with type 2 diabetes spent approximately one-third more time in the euglycemic range than women with type 1 diabetes (ratio of proportion of time in euglycemic range, 1.33 [95% CI 1.17–1.52]; $P = 0.0001$). There was extensive variability among subjects with respect to the overall duration of time spent euglycemic and the rate of change over gestation for both types of diabetes (Fig. 1*A*). The differences between type 1 and type 2 diabetes, and the changes over gestation, were very similar in magnitude when just daytime (0600–2200 h) ($P = 0.0002$ for change over time; $P = 0.0005$ for diabetes type) and nighttime (2200–0600 h) measurements were analyzed ($P = 0.0005$ for change over time; $P < 0.0001$ for diabetes type). In summary, euglycemia increased over gestation as expected but was significantly greater throughout pregnancy for type 2 diabetes.

Hyperglycemia

The increase in time spent euglycemic over gestation could be due to a decrease either in time spent hyperglycemic or time spent hypoglycemic, or both. We therefore explored the changes in patterns of hyperglycemia and hypoglycemia over gestation (Fig. 1*B* and *C*). The time spent hyperglycemic decreased with advancing gestation for women with both types of diabetes ($P = 0.007$). Women with type 2 diabetes spent only two-thirds of the amount of time hyperglycemic compared with women with type 1 diabetes (ratio of proportion of time with blood glucose level >140 mg/dl, 0.69 [95% CI 0.53–0.89]; $P = 0.005$). Furthermore, the rate of decrease was significantly greater in women with type 2 than with

type 1 diabetes ($P = 0.02$, interaction term), meaning that hyperglycemia decreased both more quickly and earlier in gestation for type 2 diabetes (Fig. 1*B*). Thus, women with type 1 diabetes showed a reduction from 41% of time spent hyperglycemic at the end of the first trimester, to 33% at the end of the third trimester, whereas the decrease between the corresponding time points for women with type 2 diabetes was from 33 to 12%. However, it should be noted that at 8 weeks' gestation, women with both types of diabetes spend >40% of the time (i.e., ~10 h/day) with a blood glucose level >140 mg/dl.

The same patterns were seen at extreme levels of hyperglycemia (glucose excursions >200 mg/dl). Extreme hyperglycemia decreased over gestation ($P = 0.0006$). Type 2 diabetes was more associated with shorter duration of extreme hyperglycemia than type 1 diabetes ($P = 0.0004$) and showed a more rapid reduction in levels through gestation ($P = 0.04$, interaction term), mirroring the above findings for milder hyperglycemia.

Hypoglycemia

Notably, the proportion of time spent hypoglycemic did not show significant change over gestation either for milder (blood glucose level <70 mg/dl, $P = 0.6$) (Fig. 1*C*) or more extreme (blood glucose level <50 mg/dl, $P = 0.1$) hypoglycemic excursions. However, women with type 1 diabetes spent more time hypoglycemic than women with type 2 diabetes (blood glucose level <70 mg/dl, $P = 0.04$; blood glucose level <50 mg/dl, $P = 0.02$), having 2.3 episodes and spending 3.3 h/day with blood glucose levels <70 mg/dl compared with 1.8 episodes and 2.3 h/day for women with type 2 diabetes. Interestingly, there were no significant differences in nocturnal hypoglycemia between women with type 1 and type 2 diabetes ($P = 0.9$ and $P = 0.2$ for blood glucose level <70 mg/dl [Fig. 1*D*] and blood glucose level <50 mg/dl, respectively), with the increased risk of hypoglycemia in women with type 1 diabetes occurring during daytime hours ($P = 0.003$ and $P = 0.009$ below each threshold). Very similar results were obtained when the number of hypoglycemic episodes and the area under the curve <70 mg/dl was analyzed (Table 1). Thus, in contrast to the results for hyperglycemia, we found that the risk of hypoglycemia did not significantly change over gestation, and although women with type 2 diabetes spend less time during the day hypoglycemic, their risk of nocturnal hypoglycemia is equivalent to that of women with type 1 diabetes.

Changes in A1C and mean blood glucose

These CGMS data therefore reveal significant differences between type 1 and type 2 diabetes in both hyperglycemia and hypoglycemia and the changes in these variables over pregnancy. Thus, we explored whether the complexity of these differences were captured by the commonly used measures of glycemic control: mean blood glucose level and A1C. Mean blood glucose level showed a significant decrease over gestation ($P = 0.009$), but showed only a trend toward lower levels in type 2 diabetes ($P = 0.08$), and did not show differences between type 1 and type 2 diabetes in the rate of change over pregnancy ($P = 0.3$, interaction term). A1C levels similarly showed significant decreases over gestation ($P = 0.004$), but showed no significant differences between type 1 and type 2 diabetes in either the overall levels ($P = 0.2$) or the rate of change over pregnancy ($P = 0.2$). It therefore appears that these overall measures of glycemia do not fully capture the striking differences in blood glucose profiles between women with type 1 and type 2 diabetes seen with CGMS.

CONCLUSIONS — This study provides the first opportunity to document the changes in glycemic patterns throughout pregnancy using the CGMS in women with both type 1 and type 2 diabetes. Unlike earlier studies, these data are longitudinal, with repeated measures, providing on average 358 h (~15 days) of continuous glucose data from each woman throughout her pregnancy. With the use of appropriate statistical methodology, this has allowed detailed analysis of the changes in several clinically relevant glycemic measures during pregnancy. These provide detailed observations regarding the duration, magnitude, and frequency of glucose fluctuations throughout pregnancy, extending previous preliminary cross-sectional data in type 1 diabetes (17,20–23) and describing the first continuous glucose data in pregnancies complicated by type 2 diabetes.

It is particularly alarming that during the critical stages of early pregnancy, women with diabetes on average spend only 50% or 12 h/day with blood glucose levels in the euglycemic range. Furthermore, despite intensive multidisciplinary team advice and support, including the use of CGMS as an educational and therapeutic tool, the proportion of time spent euglycemic has risen to only 66%, or ~16 h/day by the end of pregnancy. This is remarkably similar to a recent report in nonpregnant subjects, for whom 65% of the time was spent euglycemic, although outside pregnancy the definition of euglycemia (70–180 mg/dl) is less stringent (28). That even a population of motivated pregnant women, with "good" A1C levels, willing to wear the CGMS device, are so far from achieving euglycemia suggests that we are still a long way off from achieving the aims set out by the 1989 St. Vincent Declaration, both for women with type 1 and type 2 diabetes.

Comparisons in glycemic control between women with type 1 and type 2 diabetes

Continuous glucose monitoring demonstrated clear differences between the level of glycemic control achieved by women with type 1 and type 2 diabetes, which were not apparent from mean blood glucose or A1C measurements. Women with type 2 diabetes achieved a significantly greater reduction in hyperglycemia, beginning earlier and lasting throughout pregnancy. Indeed, the level of hyperglycemia achieved by women with type 2 diabetes by the end of the first trimester (33% of the time being >140 mg/dl) was not achieved by women with type 1 diabetes until the very end of pregnancy. It is intriguing that although women with type 2 diabetes in this study spend 33% less time hyperglycemic, even during early pregnancy, large series confirm that their risks of congenital malformation and perinatal mortality are equivalent to those of type 1 diabetes. Some authors, based on A1C measurements, have concluded that congenital malformations in type 2 diabetes are unrelated to glycemic control (3). Whereas other well-documented factors such as poor pregnancy preparation, older age, and obesity clearly contribute to the poor outcomes in type 2 diabetic pregnancies, our data nonetheless suggest that during the critical stages of organogenesis, up to 8 weeks' gestation, women with type 2 diabetes are spending as much time hyperglycemic as those with type 1 diabetes (Fig. 1*B*). The reduction in hyperglycemia achieved by the end of the first trimester may therefore be too late to reduce rates of malformation.

Glycemic control in women with type 1 diabetes

By the end of the first trimester, women with type 1 diabetes are still spending >9 h per day hyperglycemic (>140 mg/dl), with ~3 h extremely hyperglycemic (>200 mg/dl), offering an explanation for why "near-optimal glycemic control (A1C <7%) is not good enough" to prevent congenital malformation (2). Clearly, prepregnancy care plays an important role, improving early glycemic control and reducing major malformation and perinatal mortality (29). However, our recent data suggest that even the significant improvements in glycemic control achieved by women attending prepregnancy care are still "not good enough," in that they fail to reduce rates of preeclampsia and macrosomia (24,30). These complications are believed to be related to hyperglycemic excursions during the second and third trimesters (30,31), which are clearly demonstrated in this study. The majority of our subjects had near-optimal glycemic control, attended prepregnancy care, and believed that wearing CGMS was beneficial (data not shown). The modest improvements in hyperglycemia (40 to 33%) achieved by the end of pregnancy lead us to speculate that newer technologies such as real-time continuous glucose monitoring perhaps combined with insulin pump therapy, and ultimately closed loop systems, may be required to avoid hyperglycemia and reduce the risk of preeclampsia and macrosomia.

Hypoglycemia

Our study is the first to document the duration of hypoglycemia throughout pregnancy, examining the differences between daytime and nighttime hypoglycemia for women with both type 1 and type 2 diabetes. Contrary to our expectations that the amount of time spent hypoglycemic would diminish with the increasing insulin resistance of advancing gestation, we in fact found that the duration of time spent hypoglycemic remained constant throughout pregnancy, both for women with type 1 and type 2 diabetes. Of course, it is also noteworthy that the reductions in hyperglycemia were achieved without increased hypoglycemia. To preclude the vicious cycle of impaired glucose counterregulation and consequent loss of hypoglycemic warning symptoms by antecedent hypoglycemia, prevention of blood glucose level <70 mg is a recommended treatment goal (32). In our study, this was not achieved, either for women with type 1 or type 2 diabetes, despite the use of regular CGMS.

It is important to distinguish biochemical episodes of hypoglycemia from severe hypoglycemia, defined as requiring third-party assistance. The large studies required to document frequency of severe hypoglycemia consistently demonstrate increased severe hypoglycemia during the late first and/or early second trimester (32,33). Our findings show no change in the overall time spent hypoglycemic during gestation, suggesting that duration of biochemical hypoglycemia alone is not sufficient to explain this peak of severe hypoglycemia at the end of the first trimester. Although our study found a high incidence of nocturnal hypoglycemia (as suggested in earlier studies [20]), there were no differences between type 1 and type 2 diabetes in the amount of time spent hypoglycemic overnight. Surprisingly, therefore, the increased hypoglycemia for women with type 1 diabetes was limited to daytime. In nonpregnant subjects with type 1 diabetes, impaired hypoglycemic awareness predisposed to a sixfold increase in severe hypoglycemia, much of which also occurred during the waking hours (34). Further research should try, within the ethical limitations, to examine the changes in hypoglycemia awareness and glucose counterregulation during both type 1 and type 2 diabetic pregnancies.

We recognize that like all monitoring systems, CGMS is not without limitations, in particular with regard to the quality of readings during rapid blood glucose changes and in the lower hypoglycemic ranges (35). However, from this vast quantity of continuously monitored data, we have gained unprecedented insights into the magnitude, frequency, and duration of blood glucose fluctuations in women with type 1 and type 2 diabetes during pregnancy. We have demonstrated clear differences in the patterns of glycemia, with better glycemic control earlier in pregnancy for women with type 2 diabetes. Strikingly, the data highlight just how difficult it is to reach current targets for euglycemia, particularly for women with type 1 diabetes. These data are important for all clinicians seeking to limit hypoglycemia and optimize maternal glycemic control in daily practice, as well as researchers seeking to improve therapeutic interventions aimed at achieving normoglycemia during pregnancy.

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