The Effect of Glycemic Control in the Pre-Conception Period and Early Pregnancy on Birth Weight in Women With IDDM

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OBJECTIVE — To examine data from pregnancies in women with IDDM to assess the relative effects of mean glycosylated hemoglobin levels before conception, at booking, and during the 3 trimesters of pregnancy on birth weight. Good glycemic control during pregnancy in women with IDDM is important to minimize the risk of fetal malformation and macrosomia. Recent studies have suggested that glycemic control in the 1st trimester is more important than glycemic control during the 2nd or 3rd trimesters.

RESEARCH DESIGN AND METHODS — The case records of 65 deliveries to women with IDDM were reviewed. Fifty-seven deliveries were included in the present study. Of the deliveries reviewed, 32 women were in their first pregnancy and 25 women were multiparous. Only viable pregnancies were included because the major outcome variable of interest was birth weight. Glycosylated hemoglobin was recorded for each time period.

RESULTS — The median standardized birth weight was 1.1 SD higher than the nondiabetic mean. When pregnancies, in which the birth weight was greater than 1 SD above the nondiabetic mean, were compared with pregnancies, in which birth weight was less than 1 SD above the mean, significant differences were observed between the groups in HbA_1 at 6–12 months pre-conception (10.0 ± 2.3 vs. 8.6 ± 1.4%, $P = 0.02$), at 0–6 months pre-conception (10.2 ± 2.4 vs. 8.7 ± 2.0%, $P = 0.03$), at booking (9.5 ± 2.2 vs. 8.4 ± 1.6%, $P = 0.04$), and at 0–12 weeks' gestation (9.5 ± 2.2 vs. 8.0 ± 1.3%, $P = 0.04$), but HbA_1 later in pregnancy did not differ significantly between the groups. Correlational analysis of all 57 pregnancies revealed significant correlations between birth weight and HbA_1 at 0–6 months pre-conception ($r = 0.44$, $P = 0.002$), at booking ($r = 0.43$, $P = 0.001$), at 0–12 weeks' gestation ($r = 0.48$, $P = 0.001$), at 12–24 weeks' gestation ($r = 0.45$, $P = 0.001$), and at 24 weeks to term ($r = 0.34$, $P = 0.009$). However, with stepwise regression analysis, only HbA_1 at 0–12 weeks' gestation entered into the equation with a multiple r value of 0.48.

CONCLUSIONS — Glycemic control in the immediate pre-conception period and early 1st trimester appears to have a greater influence on birth weight than does glycemic control during the later weeks of pregnancy.

Pregnancy in patients with IDDM is associated with an increased risk of fetal malformation (1–6) that is related to glycemic control at the time of conception. Infants of mothers with IDDM are, on average, 500 g heavier than infants from nondiabetic pregnancies (5), and most of this extra "accelerated" fetal weight gain appears to occur from week 28 onwards (7). It has been suggested that macrosomia is in part related to poorer glycemic control and is possibly mediated by fetal hyperinsulinemia (5,8). However, the relationship between macrosomia and glycemic control is not entirely clear. Glycemic control during the last trimester of pregnancy has been considered to be important by some (1,5), although recent studies have suggested that glucose levels during the 1st trimester may be more important (9,10) and that glycosylated hemoglobin in the last trimester is only a very weak predictor of birth weight (11,12).

The aim of the present study was to examine the relative effects on birth weight of glycemic control during the pre-conception period and during the 1st, 2nd, and 3rd trimesters of pregnancy using glycosylated hemoglobin (HbA_1) as a measure of glycemic control.

RESEARCH DESIGN AND METHODS

— The case records of 65 deliveries to women with IDDM during the period from November 1992 to May 1996 at the Simpson's Memorial Maternity Pavilion of the Royal Infirmary of Edinburgh were reviewed. Fifty-seven deliveries were included in the present study. Eight cases were excluded for one of the following reasons: the women had transferred care to the Royal Infirmary halfway through the pregnancy and detailed pre-conception data were not available; insufficient data were recorded; or clinical records could not be traced. One twin pregnancy was also excluded. Of the deliveries reviewed, 32 women were in their first pregnancy and 25 women were multiparous. Only viable pregnancies were included because the major outcome variable of interest was birth weight.

Women of childbearing age were offered pre-conception counseling if they attended routine diabetes review clinics (13). During pregnancy, women were seen every 2 weeks from the time of booking, until 30 weeks' gestation and then weekly until delivery. Patients were reviewed at a joint clinic by a diabetologist, obstetrician, midwife, diabetes nurse specialist, and a dietitian. Between visits, patients were encouraged to adjust their own insulin to optimize blood glucose levels. Most women in the clinic report pregnancy very early, and almost all register by 8 weeks' gestation.

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Abbreviations: IGF-I, insulin-like growth factor I.

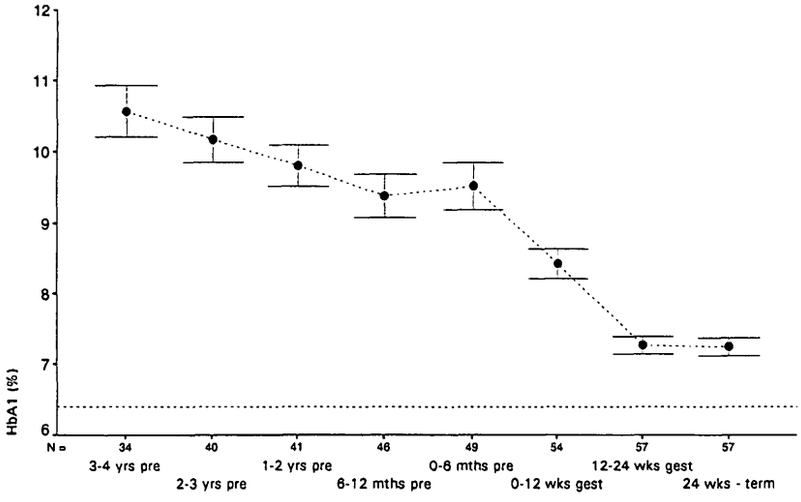

Figure 1—*Glycemic control for all deliveries (SE). Dotted line indicates the upper limit of the normal range for nondiabetic pregnancy.*

Total glycosylated hemoglobin (HbA_1) concentrations were recorded for the following time periods before pregnancy: 3–4 years, 2–3 years, 1–2 years, 6–12 months, and 0–6 months. If more than one result was available, the mean HbA_1 was taken for that period. If a patient had another pregnancy during the 4 years before the index pregnancy, data was only collected for the period 6 months after the previous delivery to minimize the effect of the previous pregnancy on glycemic control. In Edinburgh, the nondiabetic, nonpregnant normal range for HbA_1 is 5.2–6.8% and the normal range for pregnancy is 4.8–6.4% (14). HbA_1 was measured using high-speed liquid chromatography based on ion exchange reversed-phase partition method (Hi Auto A1c, HA 8121 Biomen). Although the same assay was used throughout, at the start of the study period only HbA_1 and not HbA_{1c} was documented; therefore, HbA_1 is reported for the present study.

During pregnancy, HbA_1 was measured every 2–4 weeks, and the mean HbA_1 was calculated for 0–12 weeks' gestation, 12–24 weeks' gestation, and 24 weeks to term. The lowest HbA_1 achieved at any time during the pregnancy and the gestational week at which this occurred was recorded. Birth weight and gestation at delivery were documented and adjusted according to tables produced for nondiabetic pregnancy in the hospital in which the study took place. These tables had been produced following the collection of data from 24,000 healthy women over a 5-year period. In this way, birth weights were standardized for gestational age, parity, and sex of the child and were expressed as *z*-scores.

Statistical analysis

The major outcome variable was birth weight. The deliveries were divided into two groups according to the *z*-score of the birth weight, and demographic variables and glycemic control at each time period were compared using *t* tests. Correction for multiple comparisons was not used for the comparison of glycemic control because the variables being compared were repeated measures variables. Unfortunately, it was not possible to use analysis of variance to examine these repeated measures because data was not available at every time point for all patients. The study has a greater than 80% chance of detecting a large difference (0.8 SD) between the groups ($\alpha = 0.05$). The correlational analyses using six key variables also has an 80% power of detecting a large effect ($f^2 = 0.35$).

RESULTS — Glycemic control for the whole group is shown in Fig. 1. HbA_1 at booking was 9.0 ± 1.9%. The mean lowest HbA_1 achieved was 6.7 ± 0.9%, and 26 (46%) of the women achieved an HbA_1 in the normal range for pregnancy (<6.4%) at some point during the pregnancy. Five (9%) women had achieved an HbA_1 in the nondiabetic range at booking (<6.8%). The lowest HbA_1 achieved occurred at week 23 (median).

The median gestational age at birth was 37 weeks (range 33–39 weeks). Birth weight was expressed as a *z*-score. Seven (12%) babies weighed more than 4 SD above the nondiabetic mean; 11 (19%) weighed more than 3 SD; 17 (30%) weighed more than 2 SD; and 33 (55%) weighed more than 1 SD. Only four babies weighed less than the nondiabetic mean. If a *z*-score of 1 SD above the nondiabetic mean was used as a cut point, the group was divided into two approximately equal groups. When comparing those with a *z*-score greater than 1 SD above the nondiabetic mean with those with a *z*-score less than 1 SD above the mean, significant differences in glycemic control were observed for the time periods of 1 year before conception, at the time of booking, and up to 12 weeks' gestation; however age, age at diagnosis, parity, and maternal weight and glycemic control during the later weeks of pregnancy did not differ between the groups (Table 1).

Correlational analysis of all 57 pregnancies confirmed a significant correlation between HbA_1 during the 6 months before ($r = 0.44$, $P = 0.002$), at booking ($r = 0.43$, $P = 0.001$), the first 12 weeks of pregnancy ($r = 0.48$, $P = 0.001$), weeks 12–24 of pregnancy ($r = 0.45$, $P = 0.001$), and weeks 24 to term ($r = 0.34$, $P = 0.009$) and *z*-score of the birth weight. However, because glycemic control at the different time periods was interrelated, stepwise regression analysis was performed with the *z*-score of the birth weight as the dependent variable. HbA_1 at 0–12 weeks' gestation entered at step 1 in the equation (multiple $r = 0.48$, sig $F = 0.0005$), and no other variables entered into the equation.

CONCLUSIONS — The present study has demonstrated that glycemic control assessed by glycosylated hemoglobin at the time of conception and in the early weeks of pregnancy is a more powerful predictor of birth weight than is glycemic control measured during the later weeks of pregnancy. It is important to remember that because of the lag effect in the measurement of HbA_1, each measurement really indicates glycemic control during the previous 6–8 weeks. For example, HbA_1 measured at 0–12 weeks' gestation reflects glycemic control in the immediate pre-conception period and early 1st trimester. Glycated hemoglobin measurements do not provide complete information about glycemic control; although home blood glucose measurements were performed at least four times per day by all the women, unfortunately, due to the retrospective nature of the study, this glucose data was not available.

Table 1—*Comparison of demographic variables and glycemic control between deliveries in which birth weight (z-score) was >1 SD above the nondiabetic mean and deliveries in which birth weight was <1 SD above the nondiabetic mean*

	n	*z*-score < 1 SD	*n*	*z*-score > 1 SD	*P* value
Maternal age (years)	26	29 ± 5	31	28 ± 6	NS
Maternal age at onset IDDM (years)	26	14 ± 8	31	14 ± 6	NS
Maternal weight at booking (kg)	24	66 ± 15	26	68 ± 11	NS
Glycemic control (HbA_1) (%)					
3–4 years prepregnancy	15	10.0 ± 1.7	19	11.0 ± 2.5	NS
2–3 years prepregnancy	19	9.9 ± 2.2	21	10.3 ± 1.9	NS
1–2 years prepregnancy	18	9.6 ± 1.8	23	10.0 ± 1.9	NS
6–12 months prepregnancy	21	8.6 ± 1.4	25	10.0 ± 2.3	0.02
0–6 months prepregnancy	23	8.7 ± 2.0	26	10.2 ± 2.4	0.03
Booking	25	8.4 ± 1.6	26	9.5 ± 2.2	0.04
0–12 weeks' gestation	26	8.0 ± 1.3	31	9.5 ± 2.2	0.04
12–24 weeks' gestation	26	7.1 ± 1.0	31	7.4 ± 0.9	NS
24 weeks to term	26	7.4 ± 0.8	31	7.2 ± 1.1	NS
Nadir during pregnancy	26	6.7 ± 0.9	31	6.8 ± 0.8	NS

The importance of good glycemic control at conception and during the first weeks of pregnancy in preventing fetal malformation has been well documented (3–6). The relationship between macrosomia and glycemic control is more complicated. Poor glycemic control is associated with an increased risk of macrosomia (5,8). Some of the earlier studies that have shown associations between glycemic control later in pregnancy and birth weight have not distinguished between glycemic control at the different time periods or have not measured control in the early weeks of pregnancy (1,8). Another study of both pregestational and gestational diabetic pregnancy did show an association between fasting glucose levels at 17 weeks' gestation and the incidence of macrosomia (15); however, more than half of the women had gestational diabetes, and glucose control in the very early weeks of pregnancy was not reported. Persson and Hanson (12) demonstrated that mothers with large-for-gestational-age infants had higher fasting glucose levels between weeks 27 and 32 but not earlier in pregnancy. However, correction for the effect of parity on birth weight was not performed; in addition, most of the women had relatively good glycemic control at conception, which may have masked any effect of poor glycemic control. Similarly, it cannot be excluded that the present study showed no difference in glycemic control in the last trimester between the groups because all of the women achieved glycemic control within a narrow range. Two previous studies have demonstrated results that are concordant with the findings of the present study. Peck et al. (9) showed that mothers with babies above the 90th percentile had higher HbA_1 levels at the end of the 1st trimester but not later in pregnancy. Similarly, Page et al. (10) have suggested that fructosamine levels were higher in mothers of macrosomic babies at booking, but there was no association during the later part of the pregnancy.

Two strengths of the present study are that a reasonably large number of deliveries were assessed and that women with IDDM present early in pregnancy, thereby providing data on glycemic control in early pregnancy. In addition, standardized charts for birth weight, including standardization for parity, for the clinic in which the study took place were used rather than nationally produced charts, many of which do not standardize for parity.

It is interesting to note, however, that in the present study a multiple *r* value of 0.48 suggests that glycemic control as measured by HbA_1 only contributes 23% of the variance in birth weight. Persson and Hanson (12) similarly found that only 12.3% of the variance in birth weight could be explained by blood glucose levels. In a study where excellent glycemic control was maintained throughout pregnancy, diabetic women still had an increased risk of macrosomia compared with nondiabetic subjects (11). A number of possible explanations for this have been examined and include parity, maternal age, maternal weight, smoking, presence of vascular complications, postprandial hyperglycemia, and possible genetic phenotype polymorphisms (16–20). It is possible that hyperglycemia in very early pregnancy may have an effect on the developing pancreas. Because of the inaccessibility of and risks associated with investigation of the feto-placental unit, few studies have examined the role of growth hormone and insulin-like growth factor I (IGF-I) on fetal growth (21); fetal IGF-I appears to be produced independently from the mother in the feto-placental unit (22). It is possible that early hyperglycemia may have an effect on IGF-I production, affecting early proliferative fetal development.

The clinical implications of this data emphasize the importance of good glycemic control before conception. Many studies assessing the role of the pre-conception clinic have demonstrated that there are beneficial effects on both malformation rates and birth weight outcomes (23–25). Unfortunately, because of the retrospective nature of the study, it was not possible to identify those women who had attended for pre-conception counseling. From previous studies in our clinic, the rate of attendance for pre-conception counseling is 54%. Therefore, although many women do attend pre-conception counseling, there are still a significant number of women who become pregnant with suboptimal glycemic control. A recent study has suggested that some social factors such as educational background and stability of relationships influence seeking of pre-conception care (26). Alternative methods for targeting and counseling women of childbearing age are required.

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