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Relationship between haemoglobin A_{1C} in early Type 1 (insulin-dependent) diabetic pregnancy and the occurrence of spontaneous abortion and fetal malformation in Sweden

U. Hanson[1], B. Persson[2] and S. Thunell[3]

[1] Depratment of Obstetrics and Gynaecology, Karolinska Hospital,
[2] Department of Paediatrics, St. Göran's Children's Hospital, Karolinska Institute,
[3] Department of Clinical Chemistry, St. Göran's Children's Hospital, Stockholm, Sweden

Summary. This prospective nationwide study examined the relationship between diabetic control in early pregnancy as assessed by HbA_{1C} and the incidence of spontaneous abortion and fetal malformation. HbA_{1C} and plasma C-peptide were determined in 532 women with Type 1 (insulin-dependent) diabetes mellitus, corresponding to approximately 80% of all the diabetic pregnancies in the country during the study period 1982–1985, and 222 non-diabetic control women. Median gestational week for sampling was 9.0 in the Type 1 diabetic and 10.0 in the control group. The median value of HbA_{1C} was 7.7% in the diabetic and 5.3% in the control group ($p < 0.001$). The rates of spontaneous abortion, 7.7% vs 7.2%, and malformation, 4.3% (major 2.0%) and 2.4% (major 1.0%), were not significantly different between the diabetic and control group, respectively. These rates of malformation were not significantly different from the national figures of 4.55% (major 1.75%). Much elevated HbA_{1C}, i.e., > 10.1% equal to 8 SD above the normal mean control value, was significantly associated with the occurrence of spontaneous abortion ($p < 0.001$) and malformation ($p < 0.01$). Discriminant analysis revealed that after correction had been made for the significant value of HbA_{1C} to predict the occurrence of spontaneous abortion and malformation, no further predictive power was displayed by measurable plasma C-peptide, maternal age or duration of diabetes or presence of diabetic microangiopathy. We conclude that poor metabolic control in early pregnancy contributes to an increased risk of both spontaneous abortion and fetal malformation.

Key words: Type 1 (insulin-dependent) diabetes mellitus, pregnancy, spontaneous abortion, fetal malformation, HbA_{1C}, C-peptide.

The exact cause or causes of the increased rates of malformation and spontaneous abortion in pregnancies complicated by Type 1 (insulin-dependent) diabetes are unknown [1]. The hypothesis that poor diabetic control at the time of organogenesis is an important teratogenic factor is supported by experimental studies and clinical observations of an association between elevated maternal HbA_{1C} in early pregnancy and the occurrence of malformations [2, 3]. At the time when the present investigation was started in 1982 there were only a few reports on this relationship and the published series comprised relatively small numbers and/or selected groups of patients and did not include control subjects. During the course of this study several additional investigations on the relationship between HbA_{1C} and the risk of malformation and spontaneous abortion have been reported [4–10]. These investigations raise the question of selection of the patients studied. Furthermore, with regard to the emphasis given in recent years to the importance of strict blood glucose control one may ask what are the rates of spontaneous abortion and fetal malformation in an unselected series of Type 1 diabetic pregnancies.

The object of the present study was to minimize the bias of selection and to assess in a large material the relationship between HbA_{1C} in early Type 1 diabetic pregnancy and the risk of spontaneous abortion and birth defects. The aim was also to compare the rate of malformation in offspring of Type 1 diabetic mothers with the corresponding national figures. In order to obtain a sufficiently large number of Type 1 diabetic pregnancies during a reasonable period of time a collaborative, nationwide prospective study was conducted between 1982 and 1985. Plasma C-peptide was also determined as we had previously found that women with Type 1 diabetes with some pancreatic B-cell function had better blood glucose control in early pregnancy than had patients without endogenous insulin production [11].

Subjects and methods

Study design

The present study was approved by all regional ethics committees in the country. All patients gave informed consent to participate.

The majority of pregnant women with Type 1 diabetes in Sweden are managed by specialized teams at regional or county hospitals. Altogether, 36 out of 42 hospitals were involved in the study. The selection procedure was uniform at all hospitals. Pregnant women with Type 1 diabetes were enrolled in the study at their first visit to the participating clinic, when each woman was interviewed and a venous blood sample was collected. Women whose first visit to the clinic was later than the 16th week of gestation were excluded from the study. The blood sample together with a form detailing the age of the patient, days of gestation at registration and blood collection, age at onset of diabetes, existence of proteinuria, existence and degree of retinopathy were sent to St. Göran's Hospital in Stockholm. A second venous blood sample was obtained a week later in the majority of patients with Type 1 diabetes.

A venous blood sample together with clinical data were obtained at the first visit to the antenatal clinic from non-diabetic control subjects. Recruitment of study participants lasted three years, from October 1982 until October 1985.

Patients with Type 1 diabetes

A total of 557 pregnancies were registered. Twenty patients had to be excluded because of incomplete data. An additional five pregnancies had to be excluded because of legal termination. In no case was the reason prenatal diagnosis of fetal malformation. The remaining 532 patients were included in the analyses, corresponding to approximately 180 Type 1 diabetic pregnancies each year during the study period. Maternal age and classification of maternal diabetes according to White as modified by Pedersen [12] is shown in Table 1.

Non-diabetic control subjects

A control group of 225 non-diabetic women was included. They were randomly chosen during the study period i. e. in order to assess that the procedure of HbA_{1c} determination (sampling, handling, and analysis) was kept constant. There were three legal terminations, in none was the indication fetal malformation. All control subjects received antenatal care at one maternal health care unit in Stockholm. All were subjected to a screening programme for gestational diabetes which besides traditional selection criteria for an oral glucose tolerance test also included capillary blood glucose values taken at random during each trimester of pregnancy. Gestational diabetes was not detected in any of the control women. All deliveries took place at the Department of Obstetrics and Gynaecology at the Karolinska Hospital, Stockholm, Maternal characteristics are shown in Table 1.

Registration of spontaneous abortion and fetal malformation

In all instances the pregnancy had been verified by measurement of human chorionic gonadotropin (hCG), or by ultrasound examination and/or clinical examination. Spontaneous abortion occurring after the patient's first visit to the clinic was registered. All spontaneous abortions occurred before the 20th week of gestation.

Malformations were defined as structural abnormalities detected at or soon after birth by clinical examination, X-ray or ultrasound examination. A malformation was classified as major if it was fatal or potentially life threatening or was likely to lead to serious handicap or major cosmetic defect if not surgically corrected. The remaining malformations were classified as minor. The newborn infant of the mother with Type 1 diabetes was examined by a paediatrician at delivery, the first day after delivery and at discharge from the hospital. The infants of mothers in the control group were examined by a paediatrician at least at one day of age and on discharge from the hospital at about 5–7 days. Infants with obvious or possible signs of malformation were subjected to further diagnostic procedures including X-ray and ultrasound examination. In the event of perinatal death, an autopsy was performed. Ascertainment of cardiovascular defects included X-ray and/or cardiography, cardiac catheterization and/or confirmation of the diagnosis by a paediatric cardiologist. In the total series of Type 1 diabetic and non-diabetic pregnancies, information was routinely collected from the hospital records regarding the mother's medical background, course of pregnancy, delivery and neonatal outcome.

Table 1. Maternal characteristics. According to the White's classification there were 178 class B, 142 class C, 184 class D, and 29 class F Type 1 (insulin-dependent) diabetic patients

		Type 1 diabetic women ($n = 532$)	Control women ($n = 222$)	p-value[a]
Age, year		27 (17–43)	28 (18–44)	NS
Gestational age at sampling, week	1. 2.	9 (5–16) 10 (6–17)	10.0 (7–16)	< 0.0001
HbA_{1c}, %	1. 2.	7.70 (4.3–14.4) 7.48 (4.3–12.7)	5.3 (3.5–7.1)	< 0.0001
C-peptide > 0.10 nmol/l, %		25	100	< 0.001

Values given are median and range, [a] Mann-Whitney or Chi-square test

Chemical analysis

Venous blood for determination of HbA_{1c} and C-peptide was collected in an EDTA-containing tube. HbA_{1c} was analysed by isoelectric focusing after removal of the labile fraction [13]. Normal upper limit in non-pregnant subjects is 6%. Plasma was separated and kept frozen at −20° C for later analysis of C-peptide [14]. In order to assess the influence of transportation on the analytical result, venous blood was obtained in a separate group of patients (both pregnant and non-pregnant women with Type 1 diabetes as well as non-diabetic subjects ($n = 34$)). One aliquot of the blood sample was sent by mail and another was taken directly to the laboratory for analysis of HbA_{1c} and C-peptide.

Statistical analysis

Mean, median and SD were calculated according to conventional methods. Group comparisons were analysed by the Mann-Whitney U-test. The difference between paired observations was examined by the Wilcoxon test. Group distributions were analysed by the Chi-square test with Yate's correction of Fischer's test. Association between factors was analysed by the Spearman Rank Correlation test or linear regression. Discriminant analysis was used to evaluate the influence of different factors on the occurrence of spontaneous abortion or fetal malformation.

Results

Ascertainment

On the basis of a representative 10% sample of hospital records of all diabetic pregnancies occurring between 1978 and 1981 in Sweden, we previously calculated that

there are just about 200 Type 1 diabetes pregnancies each year. From these data it was estimated that the present study included approximately 80% of the total number of Type 1 diabetes pregnancies in Sweden. The six clinics, that did not participate in the study, were evenly distributed over the country and represented both regional and county hospitals. When comparing the completed forms with the records of the participating study hospitals it was found that the 20% of patients, that were not included, mainly belonged to non-participating clinics.

Transport of samples

The levels of HbA_{1C} and plasma C-peptide in blood samples that were sent by mail were significantly correlated to values determined in samples which were brought directly to the laboratory. The correlation coefficients were $r = 0.93$ for HbA_{1C} ($p < 0.001$) and $r = 0.97$ for C-peptide ($p < 0.001$). The correlation coefficient for C-peptide values was calculated from values above or equal to 0.10 nmol/l. The mean difference between paired values of HbA_{1C} was -0.07% and for C-peptide 0.02 nmol/l. None of the paired differences were significantly different from 0.

Maternal characteristics and HbA_{1C}

The median maternal age at entry into the study did not differ significantly between the diabetic and control groups (Table 1). The venous blood samples were obtained one week earlier (median value) in the diabetic as compared to the control group. The difference is significant ($p < 0.0001$). There was also a significant difference between the two groups for HbA_{1C} ($p < 0.001$) and the number of patients with detectable C-peptide concentrations ($p < 0.001$) (Table 1) defined as the lowest C-peptide value recorded in the control group, i.e., 0.10 nmol/l. In the diabetic group there was, as expected, a highly significant ($p < 0.0001$) correlation ($r = 0.68$) between the first and second HbA_{1C} value (Table 1). The median HbA_{1C} values at the two sampling times were significantly different ($p < 0.01$). There were no significant changes in HbA_{1C} values with time in the control group. The average HbA_{1C} values for the six 6-month intervals were 5.23, 5.36, 5.20, 5.32, 5.38, and 5.19%.

Table 2. Occurrence of spontaneous abortion and fetal malformation. The rates of spontaneous abortion and malformation were not significantly different between the groups (chi-square test)

	Type 1 (insulin-dependent) diabetic women ($n = 532$)	Control women ($n = 222$)	National data 1982–1985
Spontaneous abortions	41 (7.7%)	16 (7.2%)	
Malformations Total	21 (4.3%)	5 (2.4%)	4.55%
Major	10 (2.0%)	2 (1.0%)	1.75%

Values given are number and (%)

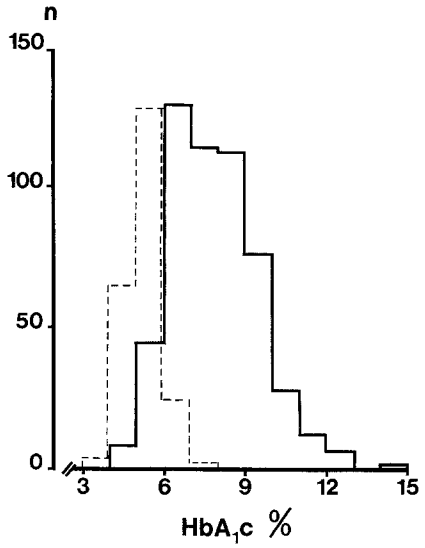

Fig. 1. Distribution of HbA_{1C} values in early pregnancy in women with Type 1 (insulin-dependent) (——) diabetes and control women (– – –)

Metabolic interrelationship

Patients with Type 1 diabetes with detectable residual B-cell function (i.e., C-peptide in plasma > 0.10 nmol/l) had a significantly ($p < 0.01$) lower median HbA_{1C} (6.8%) than those without detectable residual function (8.0%). Median C-peptide in the control group was 0.39 nmol/l. Forty-six women in the diabetic group had C-peptide levels above 0.39 nmol/l. They had significantly ($p < 0.01$) higher median maternal age (29.5 vs 27 years), significantly ($p < 0.001$) shorter median duration of diabetes (2.0 vs 13.0 years) and significantly ($p < 0.001$) lower median HbA_{1C} (6.6 vs 7.8%) compared with 486 women with plasma C-peptide levels below 0.39 nmol/l.

Incidence of spontaneous abortion and fetal malformation

The incidence of spontaneous abortion and fetal malformation in the Type 1 diabetic and control groups is summarized in Table 2 together with the national figure of major malformation for the period of 1982 to 1985. There were no significant group differences.

HbA_{1C} in relation to occurrence of spontaneous abortion or malformation

The distribution of HbA_{1C} values in patients with Type 1 diabetes and control subjects is shown in Figure 1. The HbA_{1C} values were significantly ($p < 0.001$) higher in the

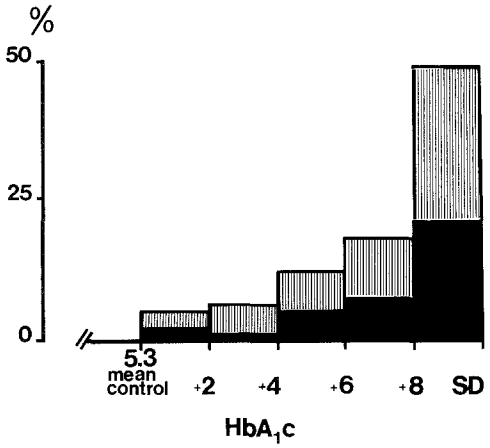

Fig. 2. Rates of spontaneous abortion (hatched area) and fetal malformation (filled area) in relation to mean HbA_{1C} value in women with Type 1 (insulin-dependent) diabetes. The HbA_{1C} values are given as standard deviations (SD) from the normal control mean value

group with Type 1 diabetes than in the control group. The HbA_{1C} values in the control group were normally distributed with a mean ± SD of 5.28 ± 0.60%. In the group with Type 1 diabetes the values were skewly distributed with a median value of 7.7%. The group of mothers with spontaneous abortion or infants with malformations had significantly higher HbA_{1C} values than those without these complications while there were no significant differences regarding maternal age, diabetic angiopathy, or number of patients with detectable plasma C-peptide values. The distribution of HbA_{1C} values in the diabetic group in relation to spontaneous abortion and malformation is given in Figure 2. A significant association was found between high HbA_{1C} (i.e., > mean + 8 SD of the control group = 10.1%) in early pregnancy and the occurrence of spontaneous abortion ($p < 0.001$) and malformation ($p < 0.01$). Maternal age, duration of diabetes and HbA_{1C} were not significantly different between the groups of Type 1 diabetic women who had infants with minor and major malformations. Both groups with major and minor malformation had significantly higher HbA_{1C} values (9.8 and 9.1%, respectively) compared with the group without spontaneous abortion or fetal malformation (7.5%) ($p < 0.01$ and $p < 0.05$, respectively). Altogether, 42 out of the 532 women with Type 1 diabetes had an initial HbA_{1C} value equal to or above 10.1%. Eleven of these 42 women (26.2%) had spontaneous abortion, nine (24%) had infants with malformation, five of which (or 16.1%) were major malformations. The remaining 22 pregnancies were uneventful. None of the maternal characteristics such as age, duration of diabetes, diabetic angiopathy, measurable C-peptide or gestational age at the time of sampling for HbA_{1C} could distinguish between the three subgroups.

Discriminant analysis revealed that after correction had been made for the significant value of HbA_{1C} for predicting the occurrence of spotaneous abortion ($p < 0.01$) and major fetal malformation ($p < 0.01$) no further predictive value was displayed by other factors, such as maternal age, duration of diabetes, angiopathy or measurable C-peptide. Discriminant analysis in the control group revealed that neither maternal age, HbA_{1C} nor C-peptide made any significant contribution to the occurrence of spontaneous abortion or fetal malformation.

Discussion

Approximately 80% of all Type 1 diabetic pregnancies were estimated to be included in this analysis suggesting that they could be regarded as representative of Sweden as a whole. The discrepancy between observed and expected numbers of diabetic pregnancies could largely be accounted for by considering the clinics that chose not to participate and to a lesser extent exclusion because of late entry into the study, i.e., beyond the 16th week of gestation. The initial blood sample was obtained around one week earlier in the diabetic as compared to the control group (i.e., median gestational week 9 vs 10), probably reflecting that women with Type 1 diabetes were aware of the importance of seeking early medical care.

The rate of malformation in the diabetic group was significantly lower than the frequency of 10.1% (major 4.8%) in Type 1 diabetic pregnancies in Sweden during the period 1978–1981. This finding of a significant decline in malformation rate is in accordance with recent observations by Mölsted-Pedersen and co-workers in Denmark [15].

Our data confirm most previous reports of a clear association between very elevated HbA_{1C} in early pregnancy and an increased risk of fetal malformations [2–4, 7, 8, 10]. A comparative evaluation of the published data suggests that when the HbA_{1C} value exceeds the mean control value by + 7 to + 10 SD or more, the rate of fetal malformation amounts to 20% or more [3, 4, 8].

Mills and co-workers found no association between maternal mean blood glucose level or HbA_{1C} values determined during the period of organogenesis and the occurrence of fetal malformation [5]. However, few of their patients had HbA_{1C} values in this very high range.

It is, however, important to emphasize that the results of the present and previous studies only demonstrate an association between very poor metabolic control and an increased risk of fetal malformation. In the individual case the HbA_{1C} value cannot be taken as an indicator of fetal malformation since, as illustrated by the present data, more than 50% of Type 1 diabetic women who had HbA_{1C} values of + 8 SD or more above the control mean value had infants without malformations.

Our data confirmed previous reports of an association between diabetic angiopathy in the mother (White's classes D and F) and a higher rate of fetal anomalies [12, 16]. However, our patients with diabetic angiopathy also had elevated HbA_{1C} values. In order to examine which variable had the greater impact on outcome, discriminant analysis was used. After correction had been made for the significant value of HbA_{1C} to predict the occurrence of spontaneous abortion and malformation, no further predictive power was displayed by diabetic angiopathy, or measurable C-peptide, maternal age or duration of diabetes.

We therefore conclude that poor blood glucose control defined as a much elevated HbA_{1C} value (> mean control + 8 SD) in early pregnancy contributes to an increased risk of both spontaneous abortion and fetal malformation. The predictive value of HbA_{1C} could not be strengthened by maternal factors like age, duration of diabetes, or presence of angiopathy.

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Dr. B. Persson
Department of Paediatrics
St. Göran's Hospital
Karolinska Institute
Box 12500
Stockholm
Sweden