

## Birth Weight and Maternal Glycated Haemoglobin in Pregnancies Complicated by Type 1 Diabetes

*D Kernaghan<sup>1</sup>, GC Penney<sup>2</sup>, DWM Pearson<sup>3</sup> on behalf of the Scottish Diabetes in Pregnancy Study Group*

<sup>1</sup>Clinical Research Fellow, Room S7130, Scottish Programme for Clinical Effectiveness in Reproductive Health, Department of Obstetrics and Gynaecology, Simpson Centre for Reproductive Health, Edinburgh Royal Infirmary, 51 Little France Crescent, Edinburgh, EH16 4SA

<sup>2</sup>Programme Director, Scottish Programme for Clinical Effectiveness in Reproductive Health, Office 66, Aberdeen Maternity Hospital, Cornhill Road, Aberdeen, AB25 2ZD

<sup>3</sup>Consultant Physician, Aberdeen Royal Infirmary, Foresterhill, Aberdeen, AB25 2ZD

### Correspondence to:

Dawn Kernaghan, Clinical Research Fellow, Room S7130 (SPCERH), Department of Obstetrics and Gynaecology, Simpson Centre for Reproductive Health, Edinburgh Royal Infirmary, 51 Little France Crescent, Edinburgh, EH16 4SA  
dawn.kernaghan@ed.ac.uk

### ABSTRACT

#### Aim

To re-examine the relationships between birth weight and maternal glycated haemoglobin (HbA1c) concentration at different time points in pregnancies complicated by pre-gestational type 1 diabetes.

#### Methods

A dataset was collected prospectively on all deliveries in Scotland to women with pre-gestational type 1 diabetes occurring during two 12 month periods (01/04/98 to 31/03/99 and 01/04/03 to 31/03/04). Relationships between standardised measures of birth weight and HbA1c at each time point were examined using correlation analysis.

#### Results

Standardised birth weights (Z scores) were calculated for 338 singleton live born infants. HbA1c concentrations were available for: 204 women (pre-pregnancy), 297 women (1st trimester), 314 women (2nd trimester) and 303 women (3rd trimester). Standardised birth weight showed a unimodal distribution shifted to the right relative to a reference population (Mean, +1.62 S.D). There was a significant negative correlation between pre-pregnancy HbA1c and birth weight (Spearman's Rho -0.138;  $p=0.049$ ).

#### Conclusions

Standardised birth weights of the infants of diabetic mothers are higher than those of a reference population. There is no simple relationship between maternal glycaemic control and birth weight, but the previously described paradoxical inverse relationship between pre-pregnancy glycaemic control and birth weight has been confirmed using a larger dataset.

### Introduction

Pregnancies in women with type 1 diabetes are more likely to be affected by a large for gestational age (LGA) infant (birth weight >95th centile for gestational age) than are pregnancies in non-diabetic women. An understanding of the pathophysiology behind this is important due to the increased risks of perinatal morbidity and mortality, and of delivery complications in these babies. Foetal growth and birth weight are determined by maternal, foetal, placental and environmental factors. Maternal glycaemic control (routinely measured using HbA1c assays) is potentially a

remediable maternal factor in these pregnancies. However, it has proved difficult to establish a consistent relationship between maternal glycaemic control and foetal size.<sup>1, 2, 3, 4, 5, 6, 7, 8</sup> We previously reported on the relationship between birth weight and maternal HbA1c in pregnancies complicated by type 1 diabetes.<sup>9</sup> In this paper, we present findings based on a larger dataset which now includes 338 women with pre-gestational type 1 diabetes.

### Methods

The methods used are those which have been published previously.<sup>9</sup> During two 12 month audit periods (1st April 1999 to 31st March 1999 and 1st April 2003 to 31st March 2004), all pregnancies among women with pre-gestational, type 1 (insulin dependent) diabetes were identified prospectively by volunteer clinicians in each of Scotland's consultant-led maternity units. Data were collected in the context of a national audit. As advised by the multi-centre research ethics committee for Scotland, formal ethical approval was not required. Our methods of data collection and processing met the requirements of the Privacy Advisory Committee of Information Services of NHS Scotland. In line with these requirements, during the second audit period, explicit written consent was obtained from women to access their clinical records and those of their babies for the purpose of the study.

Data collected for each pregnancy included up to four recorded measurements of serum glycated haemoglobin (HbA1c) in each of four time periods: pre-pregnancy (in the six months prior to conception), first trimester, second trimester and third trimester. Where a woman had more than one measurement recorded in a given time period, the lowest value was used in the analysis.

As each unit used its own assay for HbA1c, we obtained information on each hospital's quoted reference range for HbA1c in pregnant diabetic women. To allow aggregation of data, each woman's lowest HbA1c value for each time period was expressed as a percentage difference from the quoted upper limit of normal for her own maternity unit.<sup>9</sup>

Standardised birth weight scores (Z scores) were calculated based on published birth weight standards for a Scottish (Aberdeen) population<sup>10</sup> which served to correct for gestational age, sex of baby, and parity of the mother. Only pregnancies progressing to delivery of a live born singleton infant at >32 weeks gestation were included in the analysis, due to limitations of the published birth weight standards.

Our previous report related to 203 pregnancies occurring in 1998/99.<sup>9</sup> Three hundred and seventy two pregnancies were identified during the 2 audit periods. Thirty four pregnancies in the following categories were excluded from the analysis; 4 twin pregnancies, 9 perinatal deaths, 13 pregnancies ending <32 weeks, 3 pregnancies with birth weight or gestation missing preventing z scores from being calculated, and 5 second pregnancies of women featuring in both audit periods. Twelve pregnancies with major congenital anomalies were included in the final analysis in keeping with conventional reporting systems. Thus, the analysis presented in this paper relates to an updated series of 338 singleton, live born infants.

Relationships between standardised measures of birth weight and of HbA1c in different time periods were examined using correlation analysis.

## Results

Among the 338 mothers, the mean age at delivery was 29 years, 171 women (50.6%) were primigravids, the median duration of diabetes was 13 years, 83 (24.6%) were current smokers, 85 (25.1%) took the optimal 4-5mg dose of folic acid periconceptually, 108 (32%) attended for formal pre-pregnancy counselling, and 182 (53.8%) of the pregnancies were documented as planned. Among the infants, the mean standardised birth weight score was 1.62 and 143 infants (42.3%) weighed greater than the reference population 95th centile for gestational age.

Women who had pre-pregnancy HbA1c values available were more likely to have planned pregnancies 126/204 (61.8%) vs 56/134 (41.8%)  $p=0.0004$  and to have attended formal pre-pregnancy counselling 90/204

**Table 1 Standardised HbA1c (Expressed as a Percentage Difference from Quoted Hospital 'Upper Limit of Normal') in Different Time Periods and Correlation with the Standardised Birth Weight Score**

Time period	Number of cases	Percentage difference of HbA1c from hospital 'upper limit of normal'	Correlation co-efficient (Spearman's Rho)	Significance (two tailed p value)
Pre-pregnancy	204	26.9	-0.138	0.049
First Trimester	297	15.7	-0.075	0.199
Second trimester	314	1.7	0.009	0.880
Third trimester	303	4.6	0.059	0.309

(44.1%) vs 18/134 (13.4%)  $p<0.0001$  compared to those women for whom no pre-pregnancy HbA1c values were available. They were also more likely to be taking the optimal 4-5mg dose of folic acid 58/204 (28.4%) vs 27/134 (20.1%)  $p=0.0964$ .

Women who had pre-pregnancy HbA1c values available were less likely to have any degree of retinopathy. They were also less likely to be smokers 43/204 (21.1%) vs 40/134 (29.9%)  $p=0.0717$  but this difference was not statistically significant. There was no significant difference in the presence of nephropathy between the two groups.

## Discussion

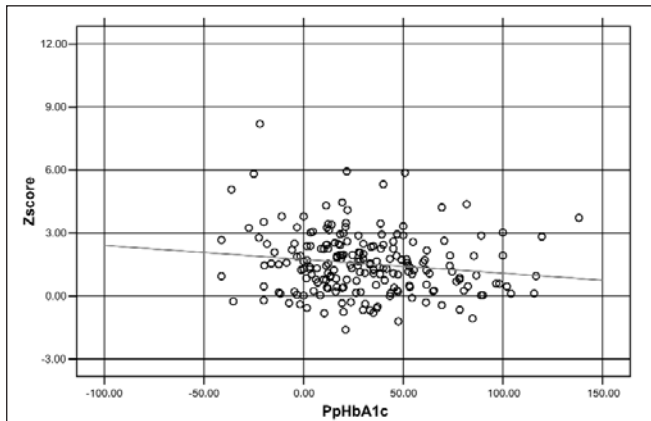
Using a larger dataset, we have confirmed our previous finding of a significant negative correlation between pre-pregnancy standardised HbA1c and standardised birth weight. However, this relationship is less strong than previously shown and again no significant correlations at other time points were seen.

Aggregating data on HbA1c levels from all centres in a country is problematic because of the different assay methods and different normal ranges used. We have attempted to overcome this difficulty by expressing each HbA1c level in terms of a percentage difference from the upper limit of normal quoted by the relevant centre. This approach was devised as a pragmatic solution to a methodological problem. We acknowledge that more rigorous statistical methods may have been applicable. However, approaches relating to the distribution of values obtained from each centre (for example, calculation of t-scores) were not feasible due to the small numbers of values available from some centres.

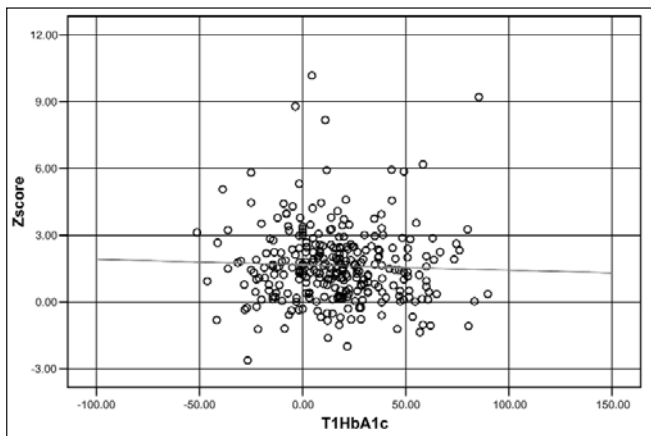
Many studies have combined data on gestational, Type 1, and Type 2 diabetes mellitus and include only small numbers of women. We have studied a large, population-

**Figure 1** Scatterplots summarising the relationships between standardised HbA1c in different time periods

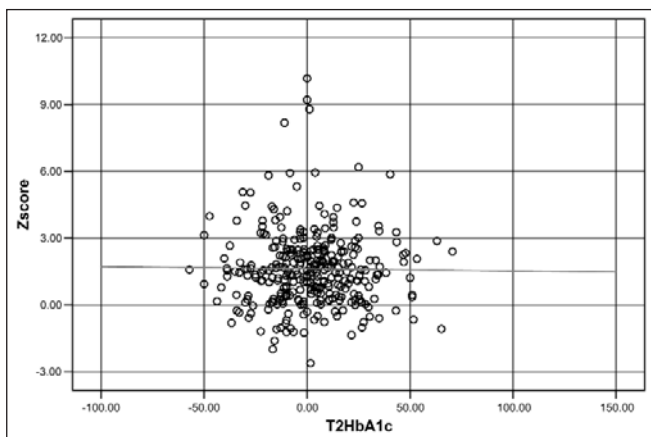
**(a) Standardised birth weight vs. standardised pre-pregnancy HbA1c**



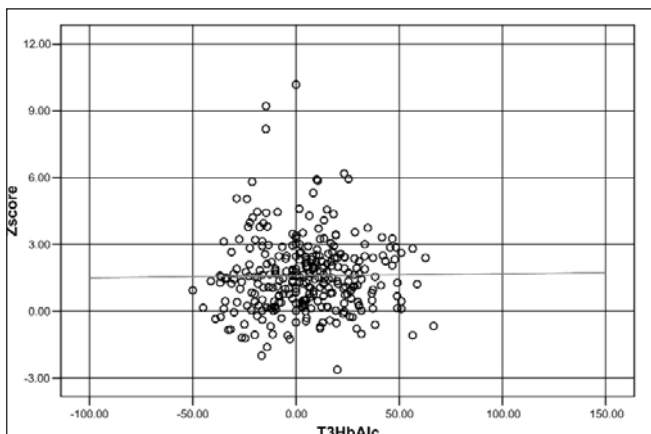
**(b) Standardised birth weight vs. standardised first trimester HbA1c**



**(c) Standardised birth weight vs. standardised second trimester HbA1c**



**(d) Standardised birth weight vs. standardised third trimester HbA1c**



based dataset of women with pre-gestational type 1 diabetes only. We acknowledge that our data on pre-pregnancy HbA1c are incomplete. Incomplete data may explain, at least in part, the correlation seen since, in some centres the pre-pregnancy records were not available to the audit teams. Those women who had pre-pregnancy HbA1c values available were more likely to have planned pregnancies and to have attended formal pre-pregnancy counselling compared to those women for whom no pre-pregnancy HbA1c levels were available. We are hypothesising that women with no pre-pregnancy HbA1c values available may have worse pre-pregnancy glycaemic control and if these results were available, and included in the analysis, the negative correlation would be more pronounced. This is supported by the fact that women with no pre-pregnancy HbA1c values available were more likely to be smokers and more likely to have microvascular disease both of which could adversely affect placental function and consequently foetal growth.

Studies examining the relationship between birth weight and HbA1c vary, with some including and some excluding congenital anomalies. Infants with congenital anomalies tend to be smaller than structurally normal infants and this is most pronounced in infants with chromosomal anomalies. Therefore, a potential explanation for the negative correlation seen between birth weight and pre-pregnancy HbA1c is that inclusion of babies with congenital anomalies – as a result of poor peri-conceptual glycaemic control – has biased the results. However, as first trimester HbA1c, rather than pre-pregnancy HbA1c, more accurately reflects pre-conceptual control and as no negative correlation is seen between first trimester HbA1c and birthweight, this is unlikely to be the case.

Therefore, having a pre-pregnancy HbA1c value available, irrespective of the value, may be a surrogate marker for some other variable, or combination of variables, which influence foetal size.

Birth weights of babies born to mothers with diabetes are subject to the same influences as babies in the rest of the population but diabetic mothers have much more variable energy substrate levels e.g glucose. Therefore, a simplistic explanation for the marked difference in birth weight between the 'diabetic' and 'non-diabetic' populations would be that glycaemic control is the important variable. This theory is compatible with the generally accepted maternal hyperglycaemia - foetal hyperinsulinaemia hypothesis.

Most studies have shown a relationship between glycaemic control and foetal size;<sup>1,3,4,5,6,7,8</sup> but the relationship is inconsistent and most authors accept that it does not explain all of the variance seen between diabetic pregnancies and those of the general population.

Johnstone et al showed that glycated HbA1c at 27-33 weeks was the strongest explanatory variable, of those analysed, affecting foetal size.<sup>4</sup> Evers et al showed that despite good glycaemic control (as measured by HbA1c) the incidence of macrosomia remained high in their population.<sup>2</sup> One possible explanation is that intermittent hyperglycaemia is a more significant contributor to the development of macrosomia than chronic hyperglycaemia.<sup>11</sup> HbA1c reflects chronic hyperglycaemia, rather than the peaks and troughs of maternal glycaemic control. Therefore, it may be too imprecise a tool to predict or explain the relationship between glycaemic control and birth weight. Other measures of glycaemic control have been investigated. Persson et al examined the relationship between birthweight and both fasting and post-prandial glucose levels.<sup>7</sup> Although raised fasting glucose levels were associated with macrosomia, this relationship pertained only when glucose levels were raised between 27-32 weeks gestation. Sturrock et al also studied blood glucose in pre-gestational diabetes and found a positive correlation between birthweight and blood glucose measures in the second and third trimesters.<sup>3</sup> No similar relationship was seen for HbA1c levels in the same group of women.

Thus, the relationship between HbA1c and birth weight cannot be easily explained. Better understanding of the pathophysiology of macrosomia and alternative measures of glycaemic control are required.

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