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ARTICLE

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Sibling birthweight as a predictor of macrosomia in women with type 1 diabetes

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Abstract *Aims/hypothesis:* The aim of this study was to establish the value of maternal HbA_1c levels and older sibling birthweight as predictors of birthweight and macrosomia in the offspring of women with type 1 diabetes. *Subjects and 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 the birthweight of the first-born infant, HbA_1c levels, maternal BMI, maternal age and time between subsequent births on the birthweight of the second-born infant. Birthweights were corrected for sex and gestational age. The percentages of first- and second-born infants with macrosomia (weight >90th centile) were calculated and compared. *Results:* Only the birthweight of earlier born infants was significantly related to that of second-born infants ($p<0.001$) and 40–50% of the variation in the birthweight of second-born infants could be explained by the birthweight of the first-born infants. About 85% of the mothers who gave birth to a macrosomic infant had a macrosomic infant in a subsequent pregnancy. *Conclusions/interpretation:* Although it is clear that glycaemic control contributes to birthweight in women with type 1 diabetes, the birthweight of an earlier born infant appears to be a much better predictor of the birthweight of a subsequent infant than HbA_1c levels during pregnancy. It may, therefore, be used to identify patients at risk of giving birth to a macrosomic infant. Daily home monitoring of glucose levels, rather than HbA_1c levels, should be used for assessment of maternal glycaemia during pregnancy.

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Introduction

Macrosomia is a frequent complication in pregnancies of women with type 1 diabetes [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 an increased risk of obesity, diabetes and breast carcinoma later in life [11, 12]. It is generally agreed that the rate of macrosomia 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 remain high [2, 4, 5]. Several studies on the relationship between HbA_1c levels and birthweight have been published [15–19]. It has proved difficult to establish a clear relationship between HbA_1c levels and infant birthweight. Positive [18, 20] and negative [19, 21] correlations have been reported between first trimester HbA_1c levels and infant birthweight, while other studies have shown that third trimester HbA_1c levels are positively related to infant birthweight [1, 2]. A constant finding of these studies is that the relationship between HbA_1c levels and infant birthweight is weak. HbA_1c levels account for <10% of the variance in the birthweight of infants of mothers with type 1 diabetes [2, 19]. This raises questions concerning the usefulness of HbA_1c levels for the prediction of foetal macrosomia in pregnant women with type 1 diabetes.

In the non-diabetic population, the birthweight of younger siblings has been shown to be correlated with that of older siblings [22, 23]. Reported correlations of sibling weight are strong, and predictive values range from 20–30% [22, 23]. In the general population, women with a macrosomic infant are ten times more likely to have a macrosomic infant in a subsequent birth than women with an

Table 1 Regression analysis of birthweight of first-born infant, HbA_1c level during the first and second halves of the second pregnancy, maternal BMI, maternal age and time elapsed between births by birthweight of second-born infant

	R	R^2	p value
Birthweight of the first-born infant[a]	0.640	0.410	0.000
	Partial correlation		p value
HbA_1c level during the first half of the second pregnancy	0.173		0.192
HbA_1c level during the second 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

[a]Expressed as a percentage of the population mean corrected for sex and gestational age

infant with a birthweight appropriate for gestational age [24]. To date, the relationship between sibling birthweights in women with type 1 diabetes has not been studied.

The aim of this study was to establish the value of HbA_1c levels and older sibling birthweight as predictors of birthweight and macrosomia in the offspring of women with type 1 diabetes mellitus.

Subjects and methods

Data on 266 pregnancies in 133 women with type 1 diabetes 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 nationwide study entitled Type 1 Diabetes Mellitus and Pregnancy in the Netherlands, 1999–2000, which was performed at our clinic [3]. The Ethics Committee of Utrecht University Medical Centre approved the nationwide 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 into 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 the birthweight of the infant [25, 26]; however, this effect seems to be smaller, or even absent, when women deliver after >37 weeks of gestation [27, 28]. In the present study, analyses were performed with and without these 15 women.

As the study was performed retrospectively, the timing and frequency of HbA_1c assessments were subject to variation; therefore, HbA_1c levels were determined by calculating the mean HbA_1c levels during the first and the second halves of the pregnancy. A standardisation procedure was adopted to adjust for variations between HbA_1c assays in different clinics [3, 29]. Each local HbA_1c value was standardised using the mean (X_N) and standard deviation (SD_N) for a local non-diabetic population. These

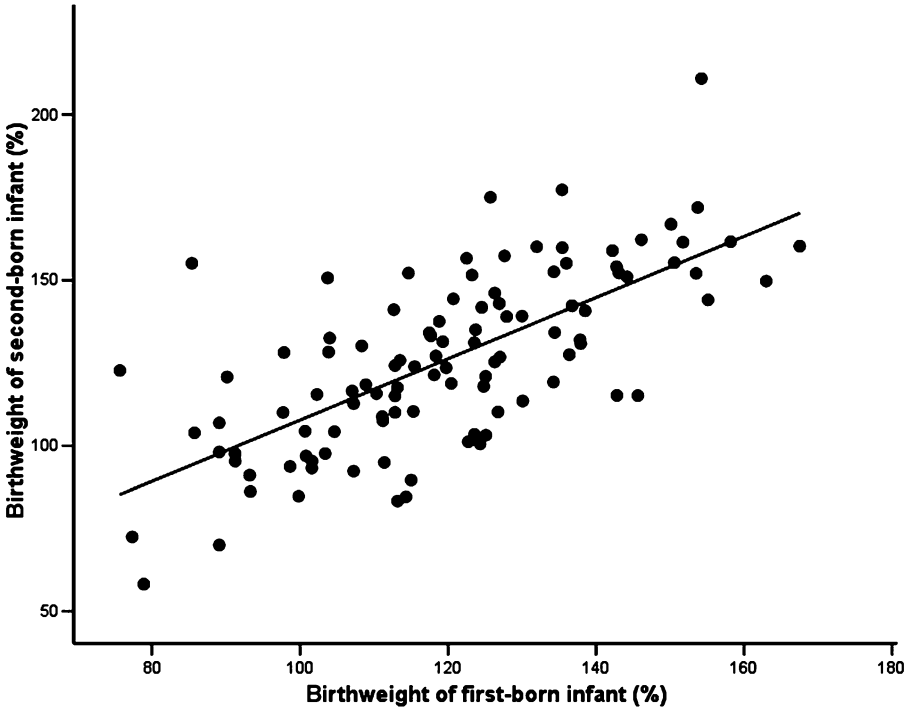

Fig. 1 Correlation between the birthweight of the first-born infant and the birthweight of the second-born infant (R=0.640, p<0.001). The birthweight of the infants is expressed as percentage of the population mean corrected for sex and gestational age

scores $[Z_{\mathrm{HbA_1c}} = (\mathrm{HbA_1c} - X_{\mathrm{N}})/\mathrm{SD_N}]$ were then transformed back into percent using the mean (5.0%) and standard deviation (0.5%) of the Utrecht assay as follows: $\mathrm{HbA_1c}$=0.5%

$$[Z_{\mathrm{HbA_1c}} = (\mathrm{HbA_1c} - X_{\mathrm{N}})/\mathrm{SD_N}] \cdot (Z_{\mathrm{HbA_1c}}) + 5.0\%$$

Birthweight was expressed as a percentage of the Dutch population mean, corrected for sex and gestational age, and as a weight centile [30]. Maternal BMI before the second pregnancy, maternal age at birth of the second child, and time elapsed between the first and second births were calculated from the data in the records.

Stepwise multiple linear regression analysis was used to evaluate the influence of the birthweight of the older

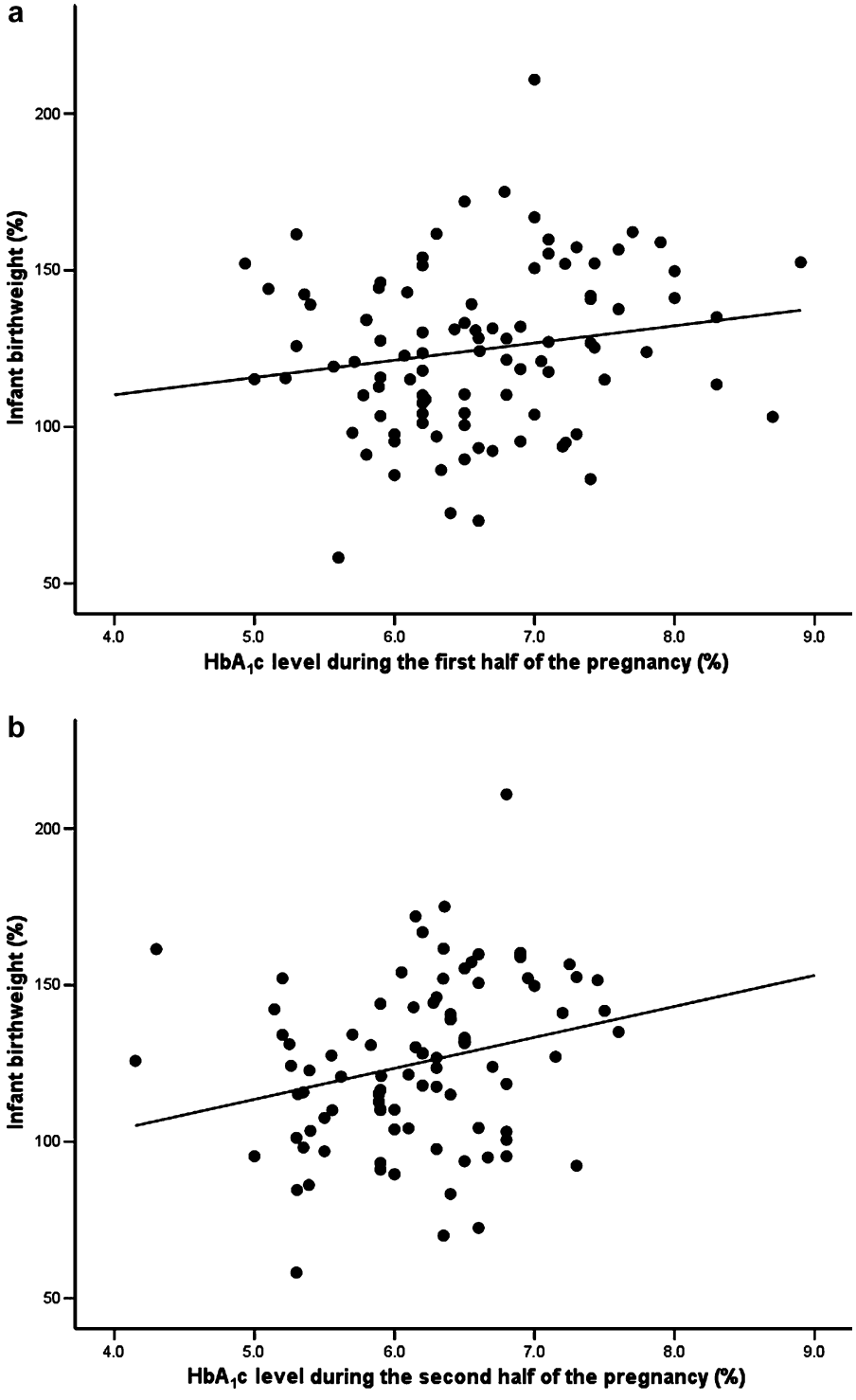

Fig. 2 Correlations between $\mathrm{HbA_1c}$ levels during the first half of the second pregnancy and the birthweight of the second-born infant (R=0.173, NS) (**a**) and between $\mathrm{HbA_1c}$ levels during the second half of the second pregnancy and the birthweight of second-born infant (R=0.251, NS) (**b**). The birthweight of the infants is expressed as percentage of the population mean corrected for sex and gestational age

Table 2 Concordance between birthweight groups of siblings of mothers with type 1 diabetes

	Second-born infant							
	Normal birthweight		Macrosomia		Severe macrosomia		Total	
	n	%	*n*	%	*n*	%	*n*	%
First-born infant								
Normal birthweight	32	68	5	11	10	21	47	100
Macrosomia (90–97.7th centile)	6	32	8	42	5	26	19	100
Severe macrosomia (≥97.7th centile)	2	5	17	10	35	85	41	100

sibling, maternal HbA_1c levels during the first and second halves of the second pregnancy, maternal BMI, maternal age, and the time elapsed between births on the birthweight of the second-born child. This analysis was repeated after the exclusion of the 15 women in whom hypertensive disorders complicated at least one of the two pregnancies.

The first-born infants were divided into three subgroups based on birthweight centiles, corrected for sex and gestational age: (1) normal weight: weight centile <p90; (2) macrosomia: weight centile p90–p97.7; and (3) severe macrosomia: weight centile ≥p97.7. For each of these groups, the percentages of second-born infants with normal weight, macrosomia and severe macrosomia were calculated. Chi-square statistics were used to test for relationships between the birthweight groups of the first-and second-born siblings. Post hoc Cramer's *V* was used to describe the strength of the relationships. For women who had an infant of normal weight and a severely macrosomic infant, HbA_1c levels during the two pregnancies were compared using Wilcoxon statistics. A *p* value of less than 0.05 was considered significant.

Results

Regression analysis revealed that the birthweight of the second-born infants was significantly related to the birthweight of the first-born infants, but not to HbA_1c level, maternal BMI, maternal age or time elapsed between births (Table 1). Figure 1 shows the relationship between the birthweight of the first-born child and the birthweight of the second-born child. Figure 2a and b show the correlation between HbA_1c levels during the first and second halves of the second pregnancy and the birthweight of the infant.

The exclusion of the 15 women with a hypertensive disorder in one or both of the pregnancies improved the correlation between the birthweights 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 birthweight within the normal range, 18% were macrosomic and 38% were severely macrosomic. Of the second-born infants, 37% had a birthweight within the normal range, 16% were macrosomic and 47% were severely macrosomic. Percentages of concordance in birthweight groups are shown in Table 2. Chi-square and Cramer's *V* statistics indicated a significant and strong association between macrosomia in the first-born infants and macrosomia in the second-born infants of women with type 1 diabetes (Cramer's V=0.507, p<0.001).

For 11 of the 12 women who had a normal weight infant and a severely macrosomic infant, the HbA_1c levels during the first pregnancy could be retrieved from the medical records (Table 3). There were no significant differences between HbA_1c levels during the first and second pregnancy in these women (p>0.8).

Table 3 HbA_1c levels during pregnancy of women who gave birth to a normal-weight infant and a severely macrosomic infant

HbA_1c levels (%)		
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 the birthweight of second-born infants of mothers with type 1 diabetes could be explained by the birthweight of the first-born infant. HbA_1c levels during pregnancy only explained 3–7% of the variation in birthweight and the HbA_1c levels of patients who had a normal-weight first-born infant and a severely macrosomic second-born infant did not differ between the two pregnancies. We, therefore, conclude that the birthweight of a previously born infant is a much stronger predictor of macrosomia than HbA_1c levels. This conclusion is supported by the finding that approximately 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 (birthweight >4000 g or >90th centile) is associated with higher rates of a prolonged first and second stage of labour and an increased risk of instrumental vag-

inal delivery, shoulder dystocia, Caesarean birth, third- and fourth-degree perineal lacerations, postpartum haemorrhage, 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 tight control is difficult to achieve and may cause maternal complications such as severe hypoglycaemia [34]. The results of the present study can be used to help to identify the multiparae who may benefit most from very tight glycaemic control.

Among the non-diabetic population, the sex of the infant, and maternal age, parity and time since last pregnancy have been shown to explain about 20% of the variance in birthweight [22]. The birthweight of the parents and maternal pre-pregnancy BMI have also been shown to correlate with the birthweight 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 the birthweight of the second-born infant. This suggests that the birthweight of offspring of women with diabetes is influenced in a different manner to that of offspring of non-diabetic women. It may be hypothesized that the birthweight of infants of mothers with diabetes is, indeed, largely influenced by glucose levels (postprandial hyperglycaemia). However, these glucose elevations are of short duration and are, therefore, not reflected accurately by HbA_1c levels, which are considered to be an indicator of mean glucose values over a 2- to 3-month period [38, 39]. Furthermore, given the strong relationship with the birthweight of an earlier-born sibling, genetic or different diabetes-related intra-uterine factors cannot be ruled out.

Because of the retrospective nature of the study, the timing and frequency of HbA_1c assessments were subject to variation. We attempted to overcome this heterogenity in the data set by using the mean HbA_1c levels during the first and second halves 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 differences in HbA_1c levels accounted for approximately 5% of the observed variation in birthweight in our study, a percentage similar to that found in previous studies [2, 19], our approach seems acceptable.

In conclusion, this study shows that HbA_1c levels are not correlated with infant birthweight. It is clear that glycaemic control contributes to infant birthweight, but that HbA_1c level is not the correct measure for the determination of glycaemia during pregnancy when related to birthweight as the endpoint. 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 birthweight is the birthweight of an earlier born infant. This measurement can be used to identify patients at risk of giving birth to a macrosomic infant; the achievement of tight glycaemic control during pregnancy is particularly important in these patients.

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