ORIGINAL ARTICLE

Course of HbA1c in non-diabetic pregnancy related to birth weight

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ABSTRACT

Background: Despite good glycaemic control (according to the internationally accepted level of HbA1c < 7% (53.0 mmol/mol)) the incidence of macrosomia in pregnant women with diabetes is still very high. We measured HbA1c levels in each of the three trimesters of pregnancy in a cohort of healthy women to determine whether the upper reference level for good glycaemic control in diabetic pregnant females should be lower than the internationally accepted level. Secondly we investigated whether changes in HbA1c values in the course of pregnancy are associated with birth weight.

Methods: We determined HbA1c by high-performance liquid chromatography in 103 healthy pregnant women. The results were corrected with a method which was certified by the National Glycohaemoglobin Standardisation Program (NGSP) and standardised to the Diabetes Control and Complication trial reference assay. All women had a body mass index (BMI) < 30, none of the women had diabetes in the family in the first and/or second degree. The multiparous women had no history of macrosomia or small for gestational age infants.

Results: In the first trimester mean ± SD (range) HbA1c (n=93) was 4.7 ± 1.25% (27.9 ± 13.7 mmol/mol) (3.9-5.4% (19.1-35.5 mmol/mol)), in the second trimester (n=86) 4.6 ± 1.33% (26.8 ± 14.6 mmol/mol) (3.7-5.7% (16.9-38.8 mmol/mol)) and in the third trimester (n=71) 4.9 ± 1.39% (30.1 ± 15.2 mmol/mol) (4.0-6.0% (20.2-42.1 mmol/mol)). The calculated upper reference HbA1c values for the three trimesters were 5.4, 5.5 and 5.8% (35.5, 36.6 and 39.9 mmol/mol), respectively, compared with 6.5% (47.5 mmol/mol) in non-pregnant women in our hospital. We found a significant correlation between the differences of the first and second trimester HbA1c values and the birth weight percentiles ($r=-0.251$; $p=0.032$). All 44 women with a decrease in the HbA1c value from the first to the second trimester had a birth weight percentile ≤90. In the 30 women with no change or an increase in the HbA1c value from the first to the second trimester there was no relation between HbA1c values and birth weight percentiles, but seven of the 30 (23.3%) had a birth weight percentile of > 90.

Conclusions: HbA1c is lower in all three trimesters of normal pregnancy compared with the level in non-pregnant women, and the change in HbA1c from the first to the second trimester predicts (the percentile of) birth weight. This could implicate that in order to prevent macrosomia in pregnant women with diabetes one should aim at lower HbA1c levels than the internationally accepted level, and at a decrease in HbA1c from the first to the second trimester.

KEYWORDS

HbA1c, pregnancy, birth weight

INTRODUCTION

Despite good glycaemic control according to the internationally accepted level of HbA1c < 7% (53.0 mmol/mol) before and during pregnancy,[1] the incidence of macrosomia in women with diabetes is still very high: 48.8%.[2] Studies disclose that HbA1c levels in healthy females are lower in pregnant than in non-pregnant women.[3] Mosca *et al.*[4] reported in a population of 445 pregnant women without diabetes and in a control group of 384 non-pregnant women a lower range in pregnant women (4.0-5.0% (20.2-31.1 mmol/mol)) than in non-pregnant women (4.8-6.2% (29.0-44.3 mmol/

mol)). This might implicate that the accepted HbA1c level in pregnancy for the prevention of macrosomia is too high. However, studies show a discrepancy in the course of HbA1c levels during the three trimesters of pregnancy. Worth *et al.*[5] and Hashimoto *et al.*[6] found an increase, Hartland *et al.*[7] and O'Kane *et al.*[8] reported no significant change, and Hanson *et al.*[9] and Gunter *et al.*[10] found a decrease. In a recent Japanese study Hiramatsu *et al.*[11] determined HbA1c in 574 pregnant and 32 non-pregnant, healthy women. HbA1c was significantly lower in the second (mean 4.9% (30.1 mmol/mol)) than in the first trimester (mean 5.2% (33.3 mmol/mol)). Mean HbA1c in the third trimester and in non-pregnant women was also 5.2% (33.3 mmol/mol), but the difference with the second trimester was not significant. The reference intervals for the groups were: 4.4-5.4% (24.6-35.5 mmol/mol), 4.7-5.7% (27.9-38.8 mmol/mol), 4.6-5.8% (26.8-39.9 mmol/mol) and 4.8-5.6% (29.0-37.7 mmol/mol), respectively.

There are several reports about the most important trimester concerning diabetic control in relation to birth weight. Gold *et al.*[12] showed that birth weight, corrected for gestational age, is best correlated with the HbA1c of 0-12 weeks of gestational age in women with type 1 diabetes. Page *et al.*[13] also suggest that macrosomia may be reduced by tighter control of diabetes at conception and in the first trimester but to a lesser extent during later stages of pregnancy. Mello *et al.*[14] found that only overall daily glucose values ≤ 95 mg/dl throughout the second and third trimesters can avoid alterations in foetal growth. Kerssen *et al.*[15] reported that in a group of women with type 1 diabetes extremely large for gestational age (LGA) infants at birth were already large before the 30th week of gestation. In these early LGA infants (foetal growth parameters ≥ 95 percentile at ≤ 30 weeks of gestation and birth weight percentile > 90), the second trimester median glucose level was significantly higher than those in the first and third trimester.

We studied a cohort of healthy, non-diabetic, pregnant women. We measured HbA1c in each trimester and investigated the influence of the change in Hba1c levels from one trimester to the other on birth weight percentiles.

MATERIALS AND METHODS

Patients

We investigated HbA1c levels in a group of healthy, pregnant women who visited the Department of Obstetrics of Leiden University Medical Centre for antenatal care between November 2002 and October 2004. The study was approved by the Ethics Committee of Leiden University Medical Centre. All subjects gave written informed consent. Excluded were women with: a body mass index (BMI) before pregnancy of ≥30, diabetes mellitus, a family history of diabetes in the first and/or second degree, hypertension, known lipid disorders, renal disease, use of corticosteroids, recurrent abortion, a history of large for gestational age (birth weight ≥ 4000 gram) and of small for gestational age infants, pre-eclampsia, preterm birth (< 34 weeks) and/or a stillbirth in a previous pregnancy. From the 130 included women, 27 (mean ± SD age: 31.9 ± 5.5 years and mean ± SD BMI (n=15): 22 ± 3) had to be withdrawn from the study: 7 due to twin pregnancy, 3 due to missed abortion, 3 due to very preterm delivery, 2 due to transfer to another hospital after the first visit and one due to termination of pregnancy because of trisomy 21. Although included, 11 women had no HbA1c measurements taken at all. Nine women were of non-Caucasian origin, but their characteristics were similar to the whole group.

HbA1c levels were measured in each trimester of pregnancy in the remaining 103 women (mean ± SD age: 31.4 ± 5.2 years and mean ± SD BMI (n=90): 23 ± 3): between 10-14 weeks, between 24-26 weeks and between 34-36 weeks in the first, second and third trimester of pregnancy, respectively. From the patients who did not complete the three measurements 7 delivered preterm, and in 39 cases blood was not sampled for logistic reasons. Overall, 57 women had three values measured, 34 two and 12 only one. HbA1c values of one woman (4.5, 4.7 and 5.4% (25.7, 27.9 and 35.5 mmol/mol), respectively) were kept out of the analysis, because she had a severely dysmature baby due to multiple congenital malformations at birth.

Between 32-36 weeks an ultrasound was performed to determine foetal growth parameters. Macrosomia was diagnosed in case of a discrepancy between foetal head (HC) and abdominal circumference (FAC) measurements: HC conform P50 and FAC > P90.

Records were kept of gestational age at time of delivery, birth weight, birth weight percentile (according to Dutch growth charts[16]), sex, mode of delivery and complications during delivery.

Analysis

We determined HbA1c levels by high-performance liquid (cation exchange) chromatography. The results were corrected with those of a boronate affinity chromatography method which was certified by the National Glycohaemoglobin Standardisation Program (NGSP) and standardised to the Diabetes Control and Complication trial reference assay.[1] The HbA1c level is given in % and SI units (mmol/mol). Pearson correlation coefficient was used to compare HbA1c levels in each trimester with birth weight percentiles. We calculated differences in HbA1c level between the first and second trimester, the first and third trimester, and the second and third trimester. We compared those differences with birth weight percentiles using the Pearson correlation coefficient.

RESULTS

HbA1c levels were normally distributed in each trimester. In the first trimester mean ± SD (range) HbA1c (n=93) was 4.7 ± 1.25% (27.9 ± 13.7 mmol/mol) (3.9-5.4% (19.1-35.5 mmol/mol)), in the second trimester (n=86) 4.6 ± 1.33% (26.8 ± 14.6 mmol/mol) (3.7-5.7% (16.9-38.8 mmol/mol)) and in the third trimester (n= 71) 4.9 ± 1.39% (30.1 ± 15.2 mmol/mol) (4.0-6.0% (20.2-42.1 mmol/mol)). In the group that completed the three measurements (n=57), the values were identical: in the first trimester 4.7 ± 1.24% (27.9 ± 13.6 mmol/mol) (3.9-5.3% (19.1-34.4 mmol/mol)), in the second trimester 4.5 ± 1.28% (25.7 ± 14.0 mmol/mol) (3.7-5.4% (16.9-35.5 mmol/mol)) and in the third trimester 4.8 ± 1.35% (29.0 ± 14.8 mmol/mol) (4.0-6.0% (20.2-42.1 mmol/mol)). We calculated the reference interval by taking the mean ± 2 x SD which includes > 95% of all measurements. The reference interval was 4.2-5.4% (22.4-35.5 mmol/mol) for the first, 3.9-5.5% (19.1-36.6 mmol/mol) for the second and 4.1-5.8% (21.3-39.9 mmol/mol) for the third trimester.

The distribution of birth weight percentiles was normal. We found no correlation between BMI before pregnancy, HbA1c value in each trimester and birth weight percentile (*table 1*).

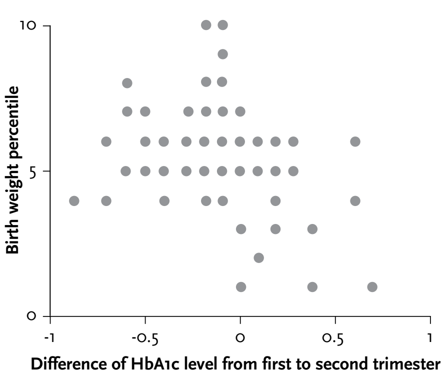
There was a significant correlation between differences of the first and second trimester HbA1c values and birth weight percentiles (*table 1*: r=-0.251; p=0.032; *figure 1*). We found no correlation between differences of the first and third trimester and of the second and third trimester HbA1c levels and birth weight percentiles (*table 1*). All 44 women with a decrease in HbA1c from the first to the second trimester had a birth weight percentile ≤ 90. In the 30 women with no change or an increase in HbA1c from the first to the second trimester, no relation was found between HbA1c and birth weight percentile, but seven of 30 infants (23.3%) had a birth weight percentile of > 90 (*table 2*).

Table 1. *Pearson correlation of different parameters with birth weight percentiles*

Parameters	Pearson correlation coefficient	p (2 tailed)
BMI (before pregnancy)	0.139	0.206
HbA1c 1st trimester	-0.030	0.978
HbA1c 2nd trimester	1.129	0.248
HbA1c 3rd trimester	-0.620	0.614
Difference 1st – 2nd trimester HbA1c	-0.251	0.032*
Difference 1st – 3rd trimester HbA1c	0.051	0.245
Difference 2nd – 3rd trimester HbA1c	0.151	0.696

***Correlation is significant at the 0.05 level (2 tailed).**

Figure 1. *Difference in % HbA1c levels from first to second trimester related to birth weight percentile*



Number	Birth weight percentile
10	≤ 2.3
9	> 2.3-5
8	> 5-10
7	> 10-25
6	> 25-50
5	> 50-75
4	> 75-90
3	> 90-95
2	> 95-97.5
1	> 97.5

Table 2. *Changes in HbA1c levels from first to second trimester related to birth weight percentiles*

Percentile	HbA1c decrease N (%)	HbA1c the same N (%)	HbA1c increase N (%)	Total N (%)
≤ 2.3	2 (100%)			2 (100%)
> 2.3-5	1 (100%)			1 (100%)
> 5-10	3 (100%)			3 (100%)
> 10-25	5 (71.4%)	1 (14.3%)	1 (14.3%)	7 (100%)
> 25-50	14 (56.0%)	3 (12.0%)	8 (32.0%)	25 (100%)
> 50-75	9 (60%)	3 (20.0%)	3 (20.0%)	15 (100%)
> 75-90	10 (71.4)		4 (28.6%)	14 (100%)
> 90-95		1 (33.3%)	2 (66.7%)	3 (100%)
> 95-97.5			1 (100%)	1 (100%)
> 97.5		1 (33.3%)	2 (66.7%)	3 (100%)
Total	44 (59.5%)	9 (12.2%)	21 (28.4%)	74 100%

All measurements were similar with and without those of the nine women of non-Caucasian origin in our sample. All women had an ultrasound estimation of the foetal weight between 32 and 36 weeks. None of the ultrasounds showed signs of macrosomia.

DISCUSSION

We found a lower upper reference HbA1c level in each trimester of pregnancy compared with the upper reference

HbA1c value of 6.5% (47.5 mmol/mol) in non-pregnant, non-diabetic women in our hospital. The level increases from 5.4% (35.5 mmol/mol) in the first trimester and 5.5% (36.6 mmol/mol) in second trimester to 5.8% (39.9 mmol/mol) in the third trimester, but never reaches 6.5% (47.5 mmol/mol). These upper reference values indicate that the internationally accepted levels of good control for diabetic pregnant women (< 7% (53.0 mmol/mol)) may be too high. To our knowledge this is the first time that a relation between a change in HbA1c and birth weight has been found in healthy, non-diabetic, pregnant women. This means that change in HbA1c level as a reflection of change in mean blood glucose value from the first to the second trimester of pregnancy is an important determinant of the ultimate birth weight. The decrease in HbA1c from the first to the second trimester found by Hiramatsu *et al.*[11] supports the importance of our data. These findings could implicate that a change in glucose levels from the first to the second trimester of pregnancy is critical to prevent LGA and macrosomic babies in pregnant women with diabetes. Kerssen *et al.*[15] investigated a group of women with type I diabetes with a continuous glucose monitoring system (CGMS) to assess the relationship between 24-hour diurnal glucose profiles in all three trimesters of pregnancy and infant birth weight. The diurnal glucose profiles show that mothers of early LGA infants (< 30 weeks) had elevated glucose levels for most of the day during the second trimester (p< 0.05). Within the group of women with early LGA infants, the second trimester median glucose level was significantly higher than that in the first and third trimester. These data support our findings concerning the importance of the second trimester glucose level in preventing macrosomia at birth. However, a more tight glycaemic control in diabetic pregnancy goes hand in hand with an increasing incidence of severe hypoglycaemia, especially in the first trimester of pregnancy.[17]

We conclude that the upper reference levels of HbA1c in the three trimesters of pregnancy in healthy, non-diabetic women are lower (5.4, 5.5 and 5.8% (35.5, 36.6 and 39.9 mmol/mol), respectively) than the level of 6.5% (47.5 mmol/mol) in our hospital in healthy, non-pregnant women. The course of HbA1c during pregnancy, especially the change from the first to the second trimester, seems to be important in predicting birth weight.

Good glycaemic control in diabetic pregnancy before and in the first trimester of pregnancy is necessary for the prevention of congenital malformations.

Special attention may also be needed for the blood glucose level in the second trimester and the change in blood glucose from the first to the second trimester in preventing macrosomia. However, until now it is difficult to achieve this desired normoglycaemia in diabetic pregnancy without an increase in severe hypoglycaemia.

More investigation is needed to confirm that besides the absolute level of HbA1c, macrosomia in diabetic pregnancy is also related to a change in the course of HbA1c during pregnancy and especially to an increase in HbA1c from the first to the second trimester.

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