

# HbA<sub>1c</sub> in healthy, pregnant women

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## ABSTRACT

**Aim:** Congenital malformations and macrosomia in infants of women with type 1 diabetes mellitus (DM1) still occur, even if diabetic control is considered 'good' (i.e. HbA<sub>1c</sub> below the nonpregnant upper reference value of 6.3%). We, therefore, measured HbA<sub>1c</sub> in healthy, pregnant women to determine whether the upper reference value for pregnant women should be lower than the nonpregnant value. **Methods:** We investigated HbA<sub>1c</sub>, measured by high-performance liquid chromatography (HPLC), in two groups of healthy primigravid women. Group 1 (n=30; 30.0 ± 5.3 (mean ± sd) years; body mass index (BMI) before pregnancy 21.7 ± 5.3 kg/m<sup>2</sup>) had a gestational age of <18 weeks (14.5 ± 2.1). Group 2 (n=32; 30.7 ± 4.9 years; BMI before pregnancy 23.2 ± 4.6 kg/m<sup>2</sup>) were >30 weeks (34.6 ± 2.5) pregnant. None of the women had diabetes in the family in the first and/or second degree. **Results:** Group 1 had an HbA<sub>1c</sub> of 4.3 ± 0.3% (range 3.9-5.0) and in group 2 the HbA<sub>1c</sub> was 4.7 ± 0.4% (range 3.6-5.9) (p<0.001). No relation was found between HbA<sub>1c</sub> and BMI vs birth weight, corrected for gestational age, within the groups. **Conclusions:** Healthy, pregnant women had a low HbA<sub>1c</sub>, particularly in the first trimester of pregnancy. This might implicate that for prevention of congenital malformations and macrosomia in pregnant DM1 women HbA<sub>1c</sub> should be below 5% in the first trimester of pregnancy and below 6% in the third trimester.

## KEYWORDS

Congenital malformations, HbA<sub>1c</sub>, healthy pregnant women, macrosomia, type 1 diabetes mellitus

## INTRODUCTION

Shortly after the introduction of insulin treatment in type 1 diabetes mellitus (DM1) in 1922, maternal mortality in pregnancy nearly decreased to the general population level, but perinatal mortality and other complications of diabetic pregnancies only diminished when diabetes control improved in the course of the years.<sup>1</sup> Greene *et al.* found an increase in major congenital malformations of 4 to 39% in diabetic pregnancies with HbA<sub>1c</sub> values above 12.7% (which is approximately equivalent to an HbA<sub>1c</sub> value of 10%) during the first trimester.<sup>2</sup> Recently the Diabetes and Pregnancy Group, France, reported results from the French multicentric survey of the outcome of pregnancy in women with pregestational diabetes showing an increase in major congenital malformations of 4.4% (twice that of the general population) in the women with an HbA<sub>1c</sub> above 8%.<sup>3</sup> However, Evers *et al.* who performed a nationwide prospective study on the risk of complications of pregnancy in women with type 1 diabetes in the Netherlands found that the incidence of all congenital malformations was already increased in pregnancies with 'excellent or good' first trimester HbA<sub>1c</sub> (<7%) to 6.3% (twice that of the general population), although the incidence was twice as high (12.9%) as that of those with nonoptimal HbA<sub>1c</sub> (>7%).<sup>4</sup> So these authors concluded that near-optimal maternal glycaemic control (HbA<sub>1c</sub> < 7%) is apparently not good enough. In an other report from this study in the Netherlands, the same authors reported that despite apparently 'good' glycaemic control (HbA<sub>1c</sub> < 7%) in type 1 diabetic pregnant women, the incidence of macrosomia was still very high.<sup>5</sup> The issue of optimal glycaemic control in diabetic pregnancy is thus still not solved. It is known that HbA<sub>1c</sub> is lower in

healthy, pregnant women, compared with the nonpregnant state, but there is discrepancy with respect to the course of HbA1c in nondiabetic pregnancy. Worth *et al.* found an increase;<sup>6</sup> Parentoni *et al.*,<sup>7</sup> Hartland *et al.*,<sup>8</sup> O’Kane *et al.*<sup>9</sup> and Nielsen *et al.*<sup>10</sup> found no significant change; Lind *et al.*,<sup>11</sup> Hanson *et al.*<sup>12</sup> and Günter *et al.*<sup>13</sup> found a decrease. We therefore measured HbA1c in healthy women in the first and third trimester of pregnancy in order to determine whether the upper reference value for pregnant women should be lower than the nonpregnant value and whether it may change during pregnancy.

## MATERIALS AND METHODS

We investigated HbA1c in two groups of healthy, primigravid women who visited the Department of Obstetrics of Leiden University Medical Centre for antenatal care. Group 1 (n=30) was less than 18 weeks pregnant and group 2 (n=32) more than 30 weeks. Age, body mass index (BMI) before pregnancy and gestational age of the women in the groups are shown in *table 1*. None of the women had diabetes in the family in the first and/or second degree. The birth weight of the 62 children, corrected for gestational age, was normal.<sup>14</sup>

HbA1c was measured by an automated determination with a high-performance liquid chromatography (HPLC) analyser.<sup>15</sup> Standard procedures were used for statistical calculations: mean  $\pm$  sd, student’s t-test for between-group comparisons, and linear regression analysis for within-group comparisons (HbA1c and BMI vs birth weight, corrected for gestational age). The study was conducted according to the Declaration of Helsinki principles. The Medical Ethical Committee of Leiden University Medical Centre approved the study. The participants of the study gave their informed consent.

## RESULTS

In group 1 the mean HbA1c ( $\pm$  sd) was 4.3 ( $\pm$  0.3)% with a range of 3.9 to 5.0%. Group 2 had a mean HbA1c ( $\pm$  sd) of 4.7 ( $\pm$  0.4)% with a range of 3.6 to 5.9% (*table 1* and *figure 1*).

The difference in HbA1c between the groups was highly significant ( $p < 0.001$ ). No relation was found between HbA1c and BMI vs birth weight, corrected for gestational age, within the groups (group 1: HbA1c vs birth weight:  $r = 0.142$ ,  $p = 0.45$  and BMI vs birth weight:  $r = -0.349$ ,  $p = 0.07$ ; group 2: HbA1c vs birth weight:  $r = 0.266$ ,  $p = 0.14$  and BMI vs birth weight:  $r = 0.318$ ,  $p = 0.08$ ).

## DISCUSSION

We found a low upper HbA1c range level of 5 % in the first trimester of pregnancy, compared with the nonpregnant upper HbA1c reference value of 6.3% in our hospital, and a higher upper HbA1c range level of 5.9% in the third trimester of pregnancy.

The low level of HbA1c in the first trimester of pregnancy is caused by the low mean preprandial and postprandial blood glucose values<sup>16</sup> and by the increase in young erythrocytes which diminishes the percentage of glycosylated haemoglobin.<sup>17</sup> The increase in HbA1c in the third trimester of pregnancy is caused by the increase in the mean postprandial blood glucose value.<sup>16</sup> This is in agreement with the findings of Monnier *et al.* who reported that in type 2 diabetic patients the relative contribution of postprandial glucose excursions to HbA1c is predominant in fairly well-controlled patients, whereas the contribution of fasting hyperglycaemia increases gradually with a worsening of the diabetes.<sup>18</sup>

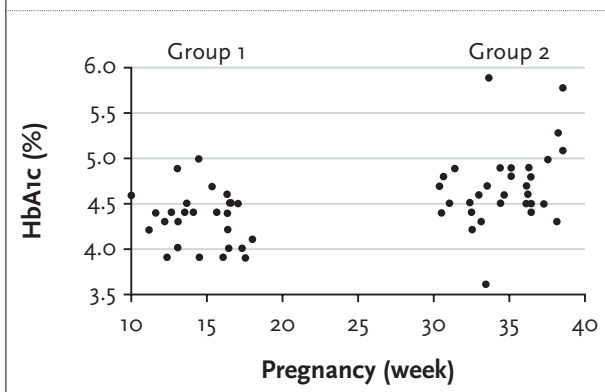
Our findings might implicate that for prevention of congenital malformations and macrosomia in diabetic pregnancies, HbA1c should be below 5.0% in the first trimester of pregnancy and below 6.0% in the third trimester. With respect to macrosomia, the recommendation of a low HbA1c in the first trimester is supported by the data of Gold *et al.* who showed that birth weight, corrected for gestational age, is best correlated with the HbA1c of 0 to 12 weeks of gestational age in women with type 1 diabetes.<sup>19</sup> So our study suggests that in order to prevent congenital malformations and macrosomia, HbA1c in the first trimester of diabetic pregnancy should be below 5.0%. However, Evers *et al.* found self-reported severe hypoglycaemia in 41% of 264 pregnant diabetic women during the first

**Table 1** Data (mean  $\pm$  sd) of age, body mass index (BMI) before pregnancy, gestational age and HbA1c of the groups

	Age (years)	BMI (kg/m <sup>2</sup> ) before pregnancy	Gestational age (weeks)	HbA1c (%) (range)
Group 1 (n=30)	30.0 $\pm$ 5.3	21.7 $\pm$ 5.3	14.5 $\pm$ 2.1	4.3 $\pm$ 0.3* (3.9-5.0)
Group 2 (n=32)	30.7 $\pm$ 4.9	23.2 $\pm$ 4.6	34.6 $\pm$ 2.5	4.7 $\pm$ 0.4* (3.6-5.9)

\*  $p < 0.001$ .

**Figure 1** HbA<sub>1c</sub> values in the first (group 1) and third trimester (group 2) of pregnancy



trimester and in 17% during the third trimester; these women had a mean HbA<sub>1c</sub> of 6.4 vs 6.7% in women who did not experience hypoglycaemia. In their study HbA<sub>1c</sub> during the first trimester was  $\leq 6.0\%$  in 32% of the women and 6.1 to 7.0% in 43%.<sup>4</sup> For the whole pregnancy, 41 and 43% of the women had an HbA<sub>1c</sub>  $\leq 6.0\%$  and 6.1 to 7.0%, respectively.

So it may be difficult to improve diabetic control during pregnancy with the current therapeutic measures without increasing the incidence of severe hypoglycaemia. Evers *et al.* reported that women on the most sophisticated therapeutic method in practice these days, the continuous subcutaneous insulin infusion, had significantly more macrosomic infants than women on treatment with multiple ( $\geq 3$ /day) daily insulin injections.<sup>5</sup> The authors argued that, in general, the reason for this could be that women with a macrosomic infant had a higher HbA<sub>1c</sub> and less episodes of severe hypoglycaemia compared with women with a nonmacrosomic infant.

Other factors could also play a role in causing complications in diabetic pregnancy. It may be possible that wide blood glucose fluctuations, which occur in diabetic pregnancy as clearly shown by the continuous glucose monitoring system,<sup>20</sup> have a deleterious effect on their own, independent of the mean blood glucose level, as reflected by the HbA<sub>1c</sub>. This is in agreement with the data of Derr *et al.* who reported that HbA<sub>1c</sub> is not affected by glycaemic instability.<sup>21</sup> Unplanned pregnancies also showed more complications, particularly congenital malformations; and pregestational hypertension and/or diabetic nephropathy are a risk for gestational hypertension and (pre)eclampsia.<sup>3,4</sup>

In conclusion, healthy, pregnant women had a low HbA<sub>1c</sub>, particularly in the first trimester of pregnancy. This might implicate that for prevention of congenital malformations and macrosomia in pregnant, type 1 diabetic women HbA<sub>1c</sub> should be below 5% in the first trimester of pregnancy and below 6% in the third trimester.

However, with the current therapeutic measures it is difficult to improve diabetic control during pregnancy to the desired level without increasing the incidence of severe hypoglycaemia. For the moment, the best treatment still seems to be multiple daily insulin injections. The search for more optimal treatment modalities of diabetic, pregnant women should have a high priority.

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