HbA_{1c} Levels Are Significantly Lower in Early and Late Pregnancy

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Strict glycemic control is essential to minimize the maternal and fetal morbidity and mortality of pregnancies complicated by diabetes (1–3). In addition to home blood glucose measurement, which may not always reflect the true average blood glucose level (4), HbA_{1c} is a useful parameter in metabolic regulation (5–8). Thus, supplementation with HbA_{1c}, as is common outside pregnancy, seems appropriate.

Before pregnancy, the target for metabolic control in women with diabetes is HbA_{1c} values near the normal range (9). However, the upper normal range of HbA_{1c} during normal pregnancy is only sparsely investigated with different methods (10), mainly in late pregnancy (5,6,11,12), and reference ranges are generally established from the nonpregnant state (4). Increased third-trimester HbA_{1c} levels are associated with an increased risk of preeclampsia (3,13), macrosomia (1), and stillbirth (2), leading to speculations that the target for HbA_{1c} in pregnancy should be even lower than outside pregnancy to prevent adverse events.

There is a need to establish the reference range of HbA_{1c} during normal pregnancy with an internationally recognized Diabetes Control and Complications Trial (DCCT)-aligned method. In this study, we evaluated the normal upper range of HbA_{1c} in early and late pregnancy.

RESEARCH DESIGN AND METHODS

— From our antenatal clinic, we randomly selected 100 healthy pregnant women without previous gestational diabetes (early pregnancy group). All subjects had a random capillary blood glucose level <7.0 mmol/l at their first antenatal visit at approximately week 14 (range 8–17), and none developed gestational diabetes. A selective screening based on risk factors for gestational diabetes was used (14).

A late pregnancy group was established of 98 healthy pregnant women in week 33 (range 28–37), who, as part of another study (14), had a normal 75-g oral glucose tolerance test (OGTT). HbA_{1c} was measured on the same day as the OGTT.

The nonpregnant control group consisted of 145 healthy women aged 30 years who were investigated as a part of the population survey Inter 99 (15). All had a normal OGTT.

All women were Nordic Caucasians and had HbA_{1c} measured in microsamples from the earlobe with the high-performance liquid chromatography DCCT-aligned method (Tosch Automated Glycohemoglobin Analyzer; Tosch Bioscience, Minato, Japan) at the Steno Diabetes Center (8) (normal range 4.1–6.4%, interassay precision coefficient of variation 3.5%). A normal OGTT was defined as a 2-h OGTT value <7.8 mmol/l (16). Random blood glucose measurements were performed using a HemoCue device (Hemocue, Ängelholm, Sweden), which has a coefficient of variation in pregnant women of 2.8–3.7% (17,18).

For calculation of BMI, prepregnancy height and weight were used in the pregnant women. The protocol was approved by the local ethical committee.

Statistical analysis

Data are given as means ± SD. A trend test was used to compare the three groups. When the trend test was significant, unpaired Student's *t* tests were used for comparison between the groups using the Bonferroni correction to allow for multiple comparisons. $P < 0.05$ is considered significant. HbA_{1c} was regarded as normally distributed. Normal range was calculated as means ± 2 SD.

RESULTS

— HbA_{1c} was significantly decreased early in pregnancy and further decreased in late pregnancy compared with age-matched nonpregnant women (Table 1). The normal range of HbA_{1c} was 4.7–6.3% in nonpregnant women, 4.5–5.7% in early pregnancy, and 4.4–5.6% in late pregnancy. To exclude that the differences in HbA_{1c} were due to differences in BMI between the groups, women with BMI >25 kg/m^2 were excluded from all the groups, leaving 106 nonpregnant subjects, 87 early pregnancy subjects, and 85 late pregnancy subjects. Average HbA_{1c} did not change significantly (control 5.5 ± 0.4, early pregnancy 5.1 ± 0.3, and late pregnancy 5.0 ± 0.3%; P for trend <0.001), whereas BMI was comparable (21.7 ± 2.0, 21.6 ± 1.7, and 21.5 ± 1.9 kg/m^2; P = NS).

CONCLUSIONS

— In carefully selected women without diabetes and using a cross-sectional design, we found that HbA_{1c} was lower early in pregnancy and further decreased in late pregnancy compared with age-matched nonpregnant women using a DCCT-aligned method. A decrease of the upper normal limit of HbA_{1c} from 6.3% before pregnancy to 5.6% in the third trimester of pregnancy is of significant clinical importance when defining the reference range for

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Abbreviations: DCCT, Diabetes Control and Complications Trial; OGTT, oral glucose tolerance test.

Table 1—*HbA_{1c} in normal, early, and late pregnancy compared with age-matched nonpregnant women without diabetes*

	Nonpregnant	Early pregnancy	Late pregnancy
n	145	100	98
Age (years)	30.0 ± 0	30.8 ± 5	29.2 ± 3
BMI (kg/m^2)	24.5 ± 4.6	23.0 ± 3.6	22.3 ± 2.8*
HbA_{1c} (%)	5.5 ± 0.4	5.1 ± 0.3†	5.0 ± 0.3†

Data are means ± SD. *Trend test $P < 0.009$. †Trend test $P < 0.0001$; nonpregnant vs. early pregnancy, $P < 0.001$; early vs. late pregnancy, $P < 0.05$; nonpregnant vs. late pregnancy, $P < 0.001$.

HbA_{1c} during pregnancy in women with diabetes.

Our findings are in agreement with O'Kane et al. (6), who studied 493 healthy women with a DCCT-aligned method, mainly in the third trimester, and with Hartland et al. (5), who investigated 267 pregnant Caucasian and 249 Asian subjects using a latex-enhanced turbidimetric immunoassay. However, nonpregnant women were not included for comparison in these two studies. Our study included a sufficient number of women to detect significant differences, and the importance of using a DCCT-aligned HbA_{1c} method has been addressed in a consensus statement (8).

In late pregnancy, all women in our study had a documented normal glucose tolerance test. This might explain why we found a further reduction in HbA_{1c} in late pregnancy in contrast to others (5).

During normal pregnancy, a decrease in fasting blood glucose occurs early in pregnancy, mainly between weeks 6 and 10, and is sustained during the remaining part of pregnancy (19). New erythrocytes formed will therefore be exposed to a lower time-averaged glucose concentration than those of nonpregnant women, and the degree of glycosylation might therefore be less (12). In addition, the erythrocyte lifespan is likely to be decreased in pregnancy, hence also reducing the HbA_{1c} value (20–22). The Hb level was not measured in this study, and a possible role of anemia could not be accounted for.

Our study, which included nonpregnant, early pregnant, and late pregnant women, demonstrated a decline of the upper normal level of HbA_{1c} from 6.3 to 5.7% in early pregnancy and to 5.6% in the third trimester of pregnancy, indicating a reduction of HbA_{1c} during normal pregnancy that is of clinical importance when defining the goal for HbA_{1c} during pregnancy complicated with diabetes.

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