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

LENE R. NIELSEN, MD[1]
PIA EKBOM, MD, PHD[1]
PETER DAMM, MD, DMSC[2]
CHARLOTTE GLÜMER, MD[3]
MERETE M. FRANDSEN[3]
DORTE M. JENSEN, MD, PHD[4]
ELISABETH R. MATHIESEN, MD, DMSC[1]

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

From the [1]Department of Endocrinology, Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark; the [2]Department of Obstetrics, Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark; the [3]Steno Diabetes Center, Copenhagen, Denmark; and the [4]Department of Endocrinology, Odense University Hospital, Odense, Denmark.

Address correspondence and reprint requests to Elisabeth Mathiesen, Department of Endocrinology, Rigshospitalet, University Hospital of Copenhagen, Blegdamsvej 9, DK-2100 Copenhagen, Denmark. E-mail: em@rh.dk.

Received for publication 19 January 2004 and accepted in revised form 20 January 2004.

C.G. holds stocks in and receives grant support from Novo Nordisk.

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.

References

1. Evers IM, de Valk HW, Mol BWJ, ter Braak EWMT, Visser GHA: Macrosomia despite good glycaemic control in type I diabetic pregnancy: results of a nationwide study in the Netherlands. *Diabetologia* 45:1484–1489, 2002
2. Lauenborg J, Mathiesen ER, Ovesen P, Westergaard JG, Ekbom P, Molsted-Pedersen L, Damm P: Audit on stillbirths in women with pregestational type 1 diabetes. *Diabetes Care* 26:1385–1389, 2003
3. Ekbom P, Damm P, Nogaard K, Clausen P, Feldt-Rasmussen U, Feldt-Rasmussen B, Nielsen LH, Molsted-Pedersen L, Mathiesen ER: Urinary albumin excretion and 24-hour blood pressure as predictors of pre-eclampsia in type I diabetes. *Diabetologia* 43:927–931, 2000
4. Kyne-Grzebalski D, Wood L, Marshall SM, Taylor R: Episodic hyperglycaemia in pregnant women with well-controlled type 1 diabetes mellitus: a major potential factor underlying macrosomia (Editorial). *Diabet Med* 16:621–622, 1999
5. Hartland AJ, Smith JM, Clark PMS, Webber J, Chowdhury T, Dunne F: Establishing trimester- and ethnic group-related reference ranges for fructosamine and HbA1c in non-diabetic pregnant women. *Ann Clin Biochem* 36:235–237, 1999
6. O'Kane MJ, Lynch PLM, Moles KW, Magee SE: Determination of a diabetes control and complications trial-aligned HbA1c reference range in pregnancy. *Clin Chim Acta* 311:157–159, 2001
7. Kilpatrick ES: Glycated haemoglobin in the year 2000. *J Clin Pathol* 53:335–339, 2000
8. Marshall SM, Barth JH: Standardization of HbA1c measurements: a consensus statement (Review). *Diabet Med* 17:5–6, 2000
9. American Diabetes Association: Preconception care of women with diabetes (Position Statement). *Diabetes Care* 23:S65–S68, 2000
10. Worth R, Potter JM, Drury J, Fraser RB, Cullen DR: Glycosylated haemoglobin in normal pregnancy: a longitudinal study with two independent methods. *Diabetologia* 28:76–79, 1985
11. Parentoni LS, de Faria EC, Bartelega MJLF, Moda VMS, Facin ACC, Castilho LN: Glycated hemoglobin reference limits obtained by high performance liquid chromatography in adults and pregnant women. *Clin Chim Acta* 274:105–109, 1998
12. Lind T, Cheyne GA: Effect of normal pregnancy upon the glycosylated haemoglobins. *Br J Obstet Gynaecol* 86:210–213, 1979
13. Hiilesmaa V, Suhonen L, Teramo K: Glycaemic control is associated with pre-eclampsia but not with pregnancy-induced hypertension in women with type I diabetes mellitus. *Diabetologia* 43:1534–1539, 2000
14. Jensen DM, Mølsted-Pedersen L, Beck-Nielsen H, Westergaard JG, Ovesen P, Damm P: Screening for gestational diabetes mellitus by a model based on risk indicators: a prospective study. *Am J Obstet Gynecol* 189:1383–1388, 2003
15. Glumer C, Jørgensen T, Borch-Johnsen K: Prevalences of diabetes and impaired glucose regulation in a Danish population. *Diabetes Care* 26:2335–2340, 2003
16. World Health Organization: *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications: Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus*. Geneva, World Health Org., 1999
17. Carr SR, Slocum J, Tefft L, Haydon B, Carpenter M: Precision of office-based blood glucose meters in screening for gestational diabetes. *Am J Obstet Gynecol* 173: 1267–1272, 1995
18. Åberg A: *Gestational Diabetes: Screening, Diagnosis and Prognosis*. Lund, Sweden, Studenterlitteratur, 2001
19. Mills JL, Jovanovic L, Knopp R, Aarons J, Conley M, Park E, Lee YJ, Holmes L, Simpson JL, Metzger B: Physiological reduction in fasting plasma glucose concentration in the first trimester of normal pregnancy: the Diabetes in Early Pregnancy Study. *Metabolism* 47:1140–1144, 1998
20. Lurie S: Age distrubution of erythrocyte population in late pregnancy. *Gynecol Obstet Invest* 30:147–149, 1990
21. Lurie S, Danon D: Life span of erythrocytes in late pregnancy. *Obstet Gynecol* 80: 123–126, 1992
22. Lurie S: Density distribution of erythrocytes in class A2 (insulin requiring) gestational diabetes. *Arch Gynecol Obstet* 258: 65–68, 1996