HbA1C but not serum glycated albumin is elevated due to iron deficiency in late pregnancy in diabetic women

Running Title: HbA1C in diabetic pregnancy with iron deficiency

Kunihiko Hashimoto MD, PhD1, Tomoaki Osugi MD, PhD1, Sanai Noguchi MD, PhD1, Yasuhiko Morimoto MD, PhD1, K ensi Wasada MD2, Shiro Imai MD, PhD2, Masako Waguri MD, PhD3, Rieko Toyoda4, Tomio Fujita MD, PhD5, Soji Kasayama MD, PhD6, Masafumi Koga MD, PhD7

From the 1Department of Internal Medicine and the 2Department of Gynecology and Obstetrics, Aizenbashi Hospital, Osaka, the 3Department of Maternal Medicine and 4Clinical Laboratory Medicine, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, the 5Fujita Clinic, Osaka, the 6Department of Medicine, Nissay Hospital, Osaka, the 7Department of Internal Medicine, Kinki Central Hospital, Hyogo, Japan

Address correspondence and reprint requests to:
Masafumi Koga, MD, PhD
E-mail: koga_m@kich.itami.hyogo.jp

Objective: We have already reported that glycated hemoglobin (HbA₁C) is elevated due to iron deficiency in late pregnancy among nondiabetic pregnant women. This report examined whether the same phenomenon is observed in pregnant women with diabetes mellitus (DM).

Research design and methods: This longitudinal study was conducted in 17 pregnant women with DM (20-35 weeks of pregnancy). HbA₁C, serum glycated albumin (GA), red blood cell indices, and iron metabolism indices were measured.

Results: HbA₁C levels were significantly increased in late pregnancy, whereas serum GA showed no significant changes. GA/HbA₁C ratio, mean corpuscular hemoglobin, serum transferrin saturation, and serum ferritin were significantly decreased in late pregnancy. Serum transferrin saturation showed a significant positive correlation with GA/HbA₁C ratio.

Conclusions: HbA₁C levels, but not serum GA levels, are elevated in late pregnancy due to iron deficiency in diabetic women. Serum GA may offer an adequate marker for glycemic control during pregnancy.
In pregnant women with diabetes mellitus (DM), namely women with gestational DM, type 2 DM, or type 1 DM, tight glycemic control during pregnancy is essential to reduce the risk of intrauterine fetal death, fetal growth abnormalities, and maternal complications (1). In patients with DM, several glycated proteins can be used as markers to evaluate glycemic control. Among them, glycated hemoglobin (HbA1C) is currently in wide use as the standard marker for clinical management of DM (2).

HbA1C is influenced not only by blood glucose levels, but also by conditions that affect red cell survival (3). Although in patients with iron-deficiency anemia HbA1C is known to be elevated (4), we recently found that HbA1C levels are also elevated in iron-deficiency states without anemia (5). Furthermore, a study in nondiabetic pregnant women on correlations between glycemic control markers [HbA1C and serum glycated albumin (GA)] and iron-deficiency status reported that in late pregnancy, HbA1C levels were increased due to iron deficiency, but serum GA levels were not influenced by such conditions (6).

Accordingly, we believed that a similar study on glycemic control markers in pregnant women with DM would be clinically important. We therefore conducted this study in pregnant women with DM.

RESEARCH DESIGN AND METHODS

This longitudinal study was conducted in 17 Japanese pregnant women with DM who were evaluated between January 2007 and August 2009 at Aizenbashi Hospital or Osaka Medical Center and Research Institute for Maternal and Child Health. Mean age of the women was 30.5±4.1 years. Category of DM for the study patients was gestational DM in 6, type 2 DM in 4, and type 1 DM in 7. Diabetes treatment was dietary therapy alone in 4 and insulin therapy in 13. During the observation period, iron and vitamin supplements were not permitted. The pregnancy period was divided into 4 terms of 4 weeks each, starting at gestational week 20: Term I, 20-23 weeks; term II, 24-27 weeks; term III, 28-31 weeks; and term IV, 32-35 weeks. In each term, HbA1C, serum GA, red blood cell (RBC) count, hematocrit, hemoglobin mean corpuscular hemoglobin (MCH), serum transferrin saturation, and serum ferritin were measured. HbA1C was measured by HPLC (ADAMS-A1c HA-8160; Arkray, Kyoto, Japan) (7) with calibration using Japan Diabetes Society (JDS) Lot 2 (8). Serum GA was determined by enzymatic methods using albumin-specific protease, ketamine oxidase and albumin assay reagent (Lucica GA-L; Asahi Kasei Pharma, Tokyo, Japan) (9). Blood cell counts, hematocrit, hemoglobin and MCH were measured using an automated hematology system. Serum ferritin concentrations were measured by chemiluminescent immunoassay (CLIA). Serum transferrin saturation was calculated by dividing serum iron by total iron binding capacity determined by calorimetric method.

RESULTS

Figure 1 shows HbA1C levels and serum GA levels in the 4 terms during pregnancy. HbA1C levels increased as pregnancy progressed, with a significant increase in late pregnancy (term I, 5.4±0.7%; term II, 5.4±0.8%; term III, 5.6±0.7%; term IV, 5.7±0.6%; p<0.05 for each of term I vs. IV and term II vs. IV; p<0.01 for term II vs. III). By contrast, serum GA levels did not change.
significantly during the 4 terms. GA/HbA$_{1C}$ ratio decreased as pregnancy progressed, with a significant decrease in late pregnancy (term I, 2.91±0.47; term II, 2.90±0.36; term III, 2.78±0.36; term IV, 2.65±0.30; p<0.05 for term I vs. term III; p<0.01 for each of term I vs. IV, term II vs. III and term III vs. IV; p<0.001 for term II vs. IV).

RBC count did not change during pregnancy, but MCH in term IV was significantly decreased (term I, 29.9±1.8 pg; term II, 29.9±2.0 pg; term III, 29.6±2.3 pg; term IV, 28.7±2.7 pg; p<0.01 for term I vs. IV, p<0.001 for each of term II vs. IV and term III vs. IV). Also, serum transferrin saturation (term I, 22.8±9.7%; term II, 19.4±10.2%; term III, 15.8±10.3%; term IV, 14.4±9.6%; p<0.05 for each of term II vs. III and term II vs. IV; p<0.01 for term I vs. II; p<0.001 for each of term I vs. III and term I vs. IV) and log-ferritin (term I, 1.35±0.58; term II, 1.06±0.64; term III, 0.81±0.64; term IV, 0.76±0.58; p<0.05 for term II vs. IV; p<0.01 for term II vs. III; p<0.001 for term I vs. II, term I vs. III and term I vs. IV) decreased as pregnancy progressed, with a significant decrease in late pregnancy (Fig. 1).

Analysis of the correlation between GA/HbA$_{1C}$ ratio and iron metabolism indices using univariate analysis showed that serum transferrin saturation showed a significant positive correlation with GA/HbA$_{1C}$ ratio (R=0.297, p=0.0214).

CONCLUSIONS
In normal pregnancy, HbA$_{1C}$ shows biphasic changes with a nadir in mid-pregnancy (10,11). The decrease in HbA$_{1C}$ levels until mid-pregnancy is thought to be due to a decline in blood glucose levels from early to mid-pregnancy. Conversely, Nielsen et al. (12) have reported that HbA$_{1C}$ levels begins to decline from early pregnancy and is further decreased in late pregnancy. In their study, whether pregnant women had iron deficiency was not investigated.

In patients with gestational DM during treatment or with a previous history of DM during pregnancy, some discrepancies between HbA$_{1C}$ levels and changes in blood glucose levels have been reported (13).

Given hemodilution seen in pregnancy, serum protein concentration decreases, and thus fructosamine levels can be influenced during pregnancy. Serum GA measures glycated albumin as a ratio of serum albumin, and so is unaffected by the serum albumin concentration. During pregnancy, GA levels have been reported to decrease slightly from early to mid-pregnancy (14). In our study, from mid-pregnancy to late pregnancy, no significant change in serum GA levels was identified. Similar results were also reported by Abe et al. (15).

Based on our findings, not only in nondiabetic pregnant women, but also in pregnant women with DM, it is important to keep in mind that iron deficiency and an increase in HbA$_{1C}$ levels can occur in late pregnancy. By contrast, serum GA levels are unaffected by iron deficiency, and thus may offer an adequate marker for monitoring glycemic control during pregnancy.
REFERENCES


FIGURE LEGENDS

**Figure 1:** Changes in HbA1c (A), serum GA (B), serum transferrin (Tf) saturation (C), and serum ferritin (log transformation) (D) during pregnancy. Term I, 20-23 weeks; Term II, 24-27 weeks; Term III, 28-31 weeks; Term IV, 32-35 weeks. * p<0.05, ** p<0.01, and *** p<0.001 vs. Term I; # p<0.05, and ## p<0.01 vs. Term II.