OBJECTIVE — A1C levels have been shown to be elevated in relation to glycemia in late pregnancy, although the precise mechanisms remain undetermined. We hypothesized that iron deficiency is involved in the A1C increase in late pregnancy.

RESEARCH DESIGN AND METHODS — In study 1, A1C, serum glycated albumin, erythrocyte indexes, and iron metabolism indexes were determined in 47 nondiabetic pregnant women not receiving iron supplementation who were divided into four groups according to gestational period (group I, 21–24 weeks; group II, 25–28 weeks; group III, 29–32 weeks; and group IV, 33–36 weeks). In study 2, these determinants were obtained at two gestational periods (20–23 weeks and 32–33 weeks) in 17 nondiabetic pregnant women.

RESULTS — In study 1, A1C levels were higher in groups III and IV than those in groups I and II, whereas serum glycated albumin levels were not different among these four groups. Hemoglobin, mean corpuscular hemoglobin (MCH), serum transferrin saturation, and serum ferritin were lower in groups III and IV. A1C levels were negatively correlated with MCH, serum transferrin saturation, and serum ferritin. In study 2, A1C levels were significantly increased at gestational weeks 32–33 from those at weeks 20–23, whereas serum glycated albumin levels did not differ between the two gestational periods. MCH, serum transferrin saturation, and serum ferritin were decreased at gestational weeks 32–33. A1C levels showed a negative correlation with MCH, serum transferrin saturation, and serum ferritin.

CONCLUSIONS — A1C levels were elevated in late pregnancy owing to iron deficiency. Serum glycated albumin may offer a better index for monitoring glycemic control in pregnancy.
In a longitudinal study (study 2), we studied 17 nondiabetic pregnant women who had been seen at Aizenbashi Hospital between February and July 2007. Their age was 28.0 ± 5.7 years. A1C, RBC count, hematocrit, hemoglobin, MCV, MCH, serum iron, serum transferrin saturation, serum ferritin, and serum glycated albumin were determined at two periods (gestational weeks 20–23 and 32–33).

For control subjects, 19 age-matched nonpregnant healthy women whose age was 27.7 ± 2.0 years were also studied.

The investigations reported here were performed in accordance with the principles of the Declaration of Helsinki as revised in 2000. The institutional review board approved this study, and all patients provided written informed consent.

**Laboratory methods**

A1C was measured by latex aggregation immunoassay using Determiner HbA1C (Kyowa Medix, Tokyo, Japan), which was found not to be influenced by hemoglobin F and other minor hemoglobin species (15), with calibration using Japan Diabetes Society Lot 2 (16). Inter- and intra-assay coefficients of variation were 0.98 and 0.97%, respectively. Serum glycated albumin was determined by enzymatic methods using albumin-specific protease, ketoamine oxidase, and albumin assay reagent (Lucica GA-L; Asahi Kasei Pharma, Tokyo, Japan) (17). Blood cell counts, hematocrit, hemoglobin, MCV, and MCH were measured by an automated hematology system. Serum iron and unsaturated iron-binding capacity were determined by a calorimetric method. Serum ferritin concentrations were measured by a chemiluminescent immunoassay method. Total iron-binding capacity and serum transferrin saturation were calculated by adding unsaturated iron-binding capacity to serum iron and dividing serum iron by total iron-binding capacity, respectively. All tests were performed in a central laboratory at Aizenbashi Hospital.

**Statistical analyses**

Data are shown as means ± SD for continuous variables and as numbers for categorical variables. Unadjusted comparisons for continuous variables were performed among groups I–IV using ANOVA, and unpaired t tests were used to compare two groups. The StatView computer program (version 5.0 for Windows; Abacus Concepts, Berkeley, CA) was used for all statistical analyses. Values of $P < 0.05$ were considered statistically significant.

**RESULTS**

Figure 1 shows A1C and glycated albumin levels in pregnant women divided into four groups according to gestational period. The results show that A1C levels were higher in groups III (29–32 weeks) and IV (33–36 weeks) than in groups I (21–24 weeks) and II (25–28 weeks). Glycated albumin during pregnancy with iron deficiency.
levels remained constant in these four groups. RBC counts did not differ among the four groups of pregnant women. However, hemoglobin, MCH, transferrin saturation, and serum ferritin levels were lower in groups III and IV (Fig. 2). A1C levels were negatively correlated with MCH, transferrin saturation, and serum ferritin (Fig. 3). Next, we studied 17 pregnant individuals at two periods during middle pregnancy (20–23 weeks) and late pregnancy (32–33 weeks). A1C levels significantly increased from middle pregnancy (4.4 ± 0.2%) to late pregnancy (4.8 ± 0.2%; *P < 0.0001), whereas serum glycated albumin levels did not change (from 13.9 ± 1.2 to 13.9 ± 1.0%; *P = 0.7029) (Fig. 4). RBC counts were unchanged during both periods (365 ± 26 × 10^6/μl in middle pregnancy vs. 367 ± 20 × 10^6/μl in late pregnancy; *P = 0.6630), whereas MCH (30.2 ± 1.5 vs. 28.8 ± 2.4 pg; *P = 0.0016), transferrin saturation (21.7 ± 10.4 vs. 12.5 ± 7.9%; *P = 0.0011), and serum ferritin (17.4 ± 14.3 vs. 5.8 ± 3.5 ng/ml; *P = 0.0022) were decreased in late pregnancy compared with values in middle pregnancy. Hemoglobin levels were also decreased but of borderline significance (from 11.0 ± 0.5 to 10.6 ± 0.9 g/dl; *P = 0.0555). When iron deficiency was defined as serum ferritin <15 ng/ml, this condition was present in 35% of women in middle pregnancy and 95% in late pregnancy. A1C levels were negatively correlated with MCH, transferrin saturation, and serum ferritin (Fig. 5).

In our study 2, the mean A1C level of 17 women in late pregnancy (32–33 weeks) was not significantly different from that of 19 age-matched nonpregnant women (4.8 ± 0.2 vs. 4.8 ± 0.2%).

**CONCLUSIONS** — We hypothesized that changes in A1C levels during pregnancy are at least partially attributable to iron deficiency, as pregnant women are often iron deficient and iron deficiency is known to influence A1C levels (14). In studies 1 and 2, MCH, serum transferrin saturation, and serum ferritin were found to be lower in pregnant women at later stages of gestation. In addition, A1C levels showed a negative correlation with MCH, serum transferrin saturation, and serum ferritin. On the basis of these observations, the increase in A1C levels in late pregnancy seems to be mainly attributable to an iron-deficient status at this period. To the best of our knowledge, this is the first study to demonstrate the involvement of iron deficiency in increased A1C levels in late pregnancy.

In both the cross-sectional study (study 1) and longitudinal study (study 2), we found that A1C levels were increased in late pregnancy. Serum glycated albumin levels, by contrast, were unchanged during the gestational course. These results suggest that the increase in A1C levels in late pregnancy is unrelated to changes in plasma glucose levels. Phelps et al. (6) have shown biphasic changes in A1C levels during pregnancy, with a nadir at gestational week 24. They also demonstrated biphasic changes in 1-h glucose levels for the 50-g oral glucose tolerance test during pregnancy, with a nadir at 20 weeks. Those results suggest that changes in plasma glucose levels are followed by changes in A1C levels during pregnancy. However, changes in plasma glucose levels were relatively small compared with changes in A1C levels. Changes in A1C levels during pregnancy may thus result from factors other than plasma glucose levels alone. In this regard, Cousins et al. (18) showed that plasma glucose levels were unchanged from middle to late pregnancy.

Supplementation with iron is recommended for pregnant women with iron deficiency anemia (10). In patients with iron deficiency anemia, A1C levels have been shown to temporarily decrease after treatment with iron (19). Thus, in patients with iron deficiency anemia, whether treated or not, A1C is inadequate as an indicator to accurately reflect glycemic control. Whether A1C levels are relatively stable in pregnant women who are continuously receiving iron supplementation from early pregnancy should be investigated.

In contrast with the results of Nielsen et al. (20) demonstrating that A1C levels were decreased early in pregnancy and

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**Figure 3** — Association of A1C levels with MCH (A), serum transferrin (Tf) saturation (B), and serum ferritin (C) in 47 pregnant women (study 1).

**Figure 4** — A1C (A) and serum glycated albumin (GA) (B) levels in 17 pregnant women (study 2) studied in middle pregnancy (20–23 weeks) and late pregnancy (32–33 weeks).
A1C during pregnancy with iron deficiency

Figure 5—Association of A1C levels with MCH (A), serum transferrin (Tf) saturation (B), and serum ferritin (C) in 17 pregnant women (study 2). ●, middle pregnancy (20–23 weeks); ○, late pregnancy (32–33 weeks).

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