

Impact of Iron Deficiency Anemia on Prevalence of Gestational Diabetes Mellitus

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OBJECTIVE— Increased Hb and ferritin have been associated with gestational diabetes mellitus (GDM). This study was performed to determine whether the prevalence of GDM is influenced by iron deficiency anemia.

RESEARCH DESIGN AND METHODS— In a retrospective case-control study, 242 women with iron deficiency anemia (Hb <10 g/dl with features of iron deficiency) were compared with 484 nonanemic women matched for year of birth, who were delivered within the same 24-month period in our hospital, with respect to maternal demographics, infant outcome, and the prevalence of GDM diagnosed according to the World Health Organization criteria.

RESULTS— There was no difference in the prepregnancy weight or BMI, but the anemic group had more multiparas and significantly lower gestational weight and BMI increments and prevalence of GDM (odds ratio [OR] 0.52, 95% CI 0.27–0.97), which was inversely correlated ($P = 0.045$) with the duration of anemia. To determine the independent effect of anemia on GDM, multiple logistic regression analysis was performed adjusting for the effects of multiparity and BMI, and anemia was confirmed to be significantly associated with decreased prevalence of GDM (adjusted OR 0.46, 95% CI 0.23–0.90).

CONCLUSIONS— The prevalence of GDM is reduced in iron deficiency anemia, which probably served as a surrogate for other factors such as nutritional inadequacy and reduced gestational weight gain. Further studies on the relationship between nutritional improvement and the increasing prevalence of GDM in the developing world are warranted.

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Many studies have shown that high as well as low maternal antenatal Hb concentrations are associated with increased pregnancy complications and adverse outcome (1–6), but none had included gestational diabetes mellitus (GDM) as one of the outcomes.

Recently, a case-control study in overweight Chinese women found that those with mild gestational glucose intolerance in form of the World Health Organization (WHO) category of impaired glucose tolerance (7) had significantly increased Hb concentration compared with

control subjects matched for BMI (8). Another study in Chinese women without underlying hemoglobinopathies also demonstrated that maternal Hb concentration >13 g/dl in the first antenatal visit is an independent risk factor for GDM (9). In fact, nonpregnant diabetic subjects have been found to have increased total red cell count compared with age- and sex-matched control subjects (10). In men, Hb was significantly related to the incidence of diabetes (11). In women, Hb was positively and significantly related to fasting glucose, and red cell count was

positively related to glucose intolerance (12–14). Therefore, the association between high Hb with glucose intolerance may represent a universal phenomenon and be independent of sex or pregnancy status.

On the other hand, little is known about the relationship between anemia with diabetes or GDM. A study in the Chinese population has found that there was no apparent difference in the incidence of GDM between anemic and nonanemic women (15). However, when the type of anemia was further analyzed, women with iron deficiency anemia had about one-half the incidence of GDM compared not only with nonanemic women but also with women with anemia due to thalassemia traits. To determine whether the prevalence of GDM is indeed influenced by the presence and duration of iron deficiency anemia, we performed this retrospective case-control study in women carrying singleton pregnancies and delivered in our hospital over a 24-month period.

RESEARCH DESIGN AND METHODS

Our hospital is a government-funded regional referral center with ~5,000 deliveries per annum and caters mainly to residents of Hong Kong who receive free antenatal care. Most of our patients (95%) are ethnic Chinese. A multivitamin preparation containing 29 mg of elemental iron is prescribed to all patients from first (booking) antenatal visit, but patients' compliance is not monitored. At the booking visit, maternal Hb concentration, mean cell volume (MCV), and blood group are checked routinely. Those with MCV <80 fl undergo Hb electrophoresis and examination of the blood smear for Hb-H inclusion bodies, and the partner also has MCV screening. If both partners have low MCV, prenatal diagnosis is offered to determine whether the fetus is affected by homozygous α - or β -thalassemia, for which termination of pregnancy would be arranged. Patients with Hb level <10 g/dl at any time during pregnancy are considered to have anemia,

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Abbreviations: GDM, gestational diabetes mellitus; LGA, large for gestational age; MCV, mean cell volume; SGA, small for gestational age; WHO, World Health Organization.

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Table 1—Maternal and infant characteristics between the anemic and nonanemic groups

	Anemic	Nonanemic	P
n	242	484	
Maternal age (years)	27.9 ± 5.4	28.4 ± 4.8	NS
Multiparas (%)*	55.6	45.3	0.009
Height (cm)	152.6 ± 5.8	155.4 ± 5.3	<0.0001
Weight (kg)			
Prepregnant	51.6 ± 9.2	51.9 ± 7.1	NS
Predelivery	61.7 ± 9.7	65.0 ± 8.4	<0.0001
Weight gain (kg)	10.4 ± 4.4	13.1 ± 4.4	<0.0001
BMI (kg/m ²)			
Prepregnant	21.9 ± 2.6	21.5 ± 2.7	0.051
Predelivery	26.4 ± 3.0	26.9 ± 3.2	0.034
BMI increment (kg/m ²)	4.5 ± 2.0	5.4 ± 1.8	<0.0001
Incidence of GDM (%)*	5.3	9.8	0.038
Infant gestation (weeks)	38.8 ± 1.8	39.1 ± 1.5	NS
Birth weight (g)	3,236 ± 438	3,169 ± 447	0.053
Crown heel length (cm)	50.3 ± 2.2	49.7 ± 2.6	NS
BMI (kg/m ²)	12.8 ± 1.5	12.8 ± 1.2	NS
Apgar score			
At 1 min	8.8 ± 1.1	8.7 ± 1.2	NS
At 5 min	9.8 ± 0.5	9.8 ± 0.8	NS
Incidence of LGA (%)*	21.5	12.8	0.002
Incidence of SGA (%)*	4.1	7.5	0.073

Data are means ± SD or percent. Analysis was performed by Student's *t* test or χ^2 test (indicated by asterisks).

and empirical treatment is usually commenced pending the results of the investigation. At 28–30 weeks, the Hb level is repeated to identify patients in whom anemia has subsequently developed. The management of anemia in our hospital has been described before (15).

In the antenatal clinic, the 75-g oral glucose tolerance test, as interpreted by the original WHO criteria (7), is arranged before 18 weeks' gestation for women with risk factors for GDM, including maternal age >34 years, relevant past obstetric and family history, obesity, and recurrent and/or significant glycosuria. We include under GDM both the categories of impaired glucose tolerance (2-h glucose value ≥ 8.0 mmol/l) and diabetes (2-h value ≥ 11.0 mmol/l), as recommended (7). At 30–32 weeks, the oral glucose tolerance test is repeated for high-risk women with previous normal results, as well as for low-risk women with increased random glucose values (>5.8 mmol/l for <2 h postprandial and >5.0 mmol/l for >2 h postprandial) at screening at 28–30 weeks. Women in whom GDM is diagnosed are put on diet control (30 kcal/kg) and then assessed with 2-h postprandial blood glucose profile. The management of GDM in our hospital has been described before (8,9).

In this retrospective case-control study, we retrieved from the annual statistics the patients carrying singleton pregnancies coded as having antenatal anemia and delivered within a 24-month period. Included in the final study cohort were those with a diagnosis of iron deficiency confirmed by iron studies, Hb electrophoresis studies, and/or response to iron therapy and booking before 20 weeks' gestation. Excluded were women with other causes of anemia such as thalassemia trait and those who had late booking or delivery elsewhere. For each index woman, two control subjects without anemia matched for the year of birth, who carried singleton pregnancies and delivered in the same period, were selected at random from the delivery suite registry. Women who had late booking or were recorded as vegetarians were excluded. The two groups were compared for maternal demographics, gestational weight gain, incidence of GDM, Hb, and MCV, and pregnancy outcome, which included the incidence of large for gestational age (LGA) infants (birth weight >90th percentile according to our hospital population reference chart) and small for gestational age (SGA) infants (birth weight ≤ 10 th percentile). The relationship between anemia and GDM was fur-

ther analyzed according to the duration and timing of anemia, because the effect of anemia on pregnancy outcome is suggested to be related to the gestation at diagnosis (16). However, maternal iron status was not used to classify the severity of anemia in this study because of the inevitable and variable delay between the time of investigation with the time of Hb measurement, as well as the possible confounding effect of the routine multivitamin preparation prescribed at booking. Instead, we have compared the MCV, which is strongly correlated with maternal ferritin concentration (17) and can be a surrogate for maternal iron status (18). For statistical analysis, categorical variables were compared with the χ^2 test and correlation between the prevalence of GDM was tested by Pearson's correlation. Odds ratios (ORs) with 95% CI were generated as indicated. Continuous variables that are normally distributed were expressed as mean ± SD and tested by the Student's *t* test. Statistical calculation was performed using a commercial computer package (Statistical Package for Social Sciences for Windows version 10.0; SPSS, Chicago, IL).

RESULTS— Of the 287 case subjects with a label of iron deficiency anemia, 45 were excluded after a review of the records for the aforementioned reasons. The study group of 242 women was shorter, had lower predelivery weight and BMI with concomitant decreased gestational weight gain and BMI increment, and had more multiparas but a lower prevalence of GDM (OR 0.52, 95% CI 0.27–0.97). (Table 1). All 12 cases of GDM in the study group belonged to the WHO category of impaired glucose tolerance, whereas 2 of the 46 cases of GDM in the control group belonged to the WHO category of diabetes. There were no apparent differences in the infant outcome; however, the study group had a higher prevalence of LGA infants (1.87, 1.25–2.80).

When the Hb and MCV were analyzed, the Hb values at booking, early third trimester, and before delivery were all significantly lower in the study group, as expected (Fig. 1). Similarly, the corresponding MCV values were also significantly lower.

To examine the relationship between the timing and duration of the anemia and the prevalence of GDM, the study group

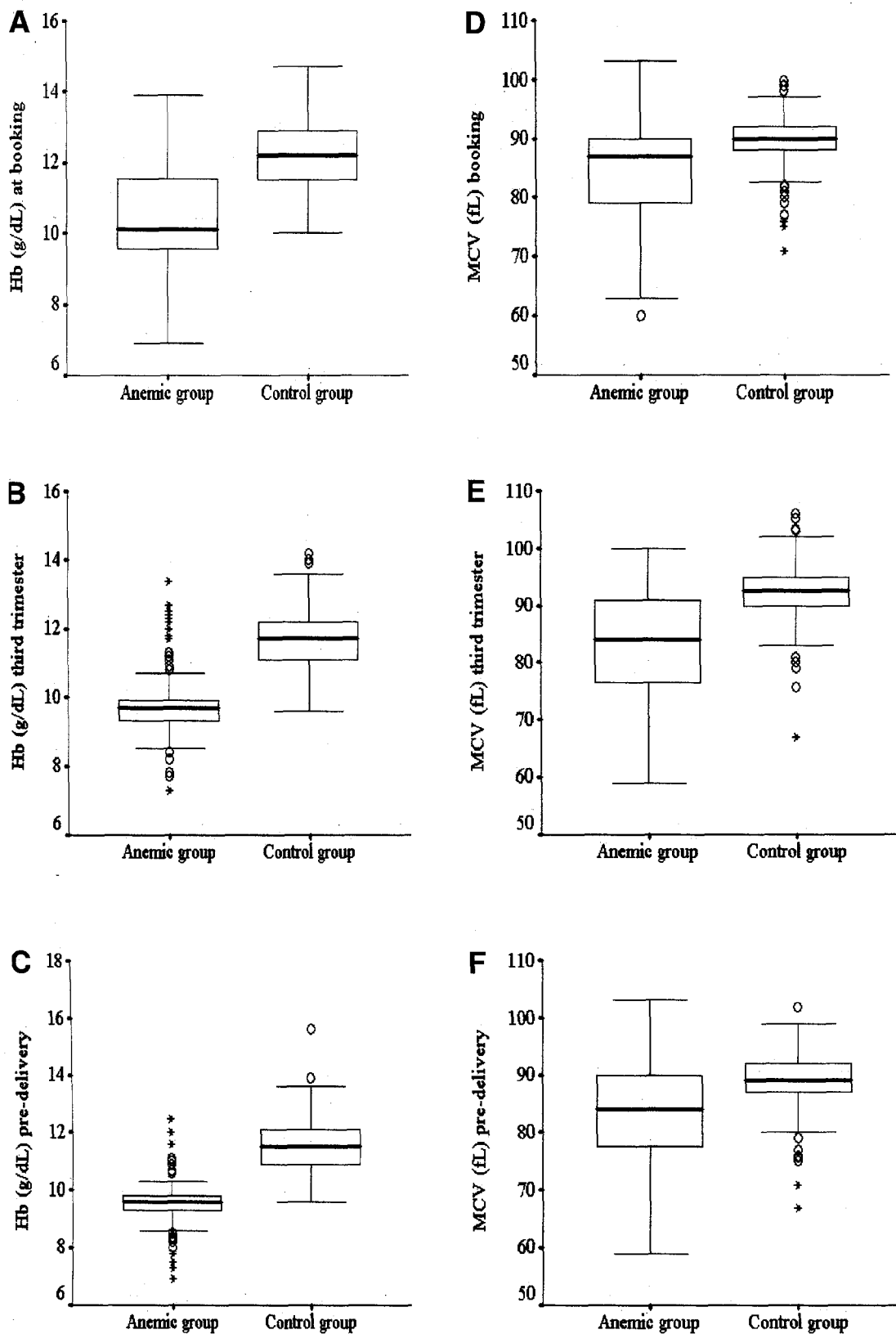


Figure 1—Box-whisker plots of maternal Hb and MCV values in the anemic and nonanemic control groups. A, B, and C: Hb concentrations. D, E, and F: MCV values at booking, third trimester, and pre-delivery, respectively. ○, outlying values; *, extreme outlying values. Comparison by Student's t test; $P < 0.0001$ in all cases.

Table 2—Maternal characteristics according to duration of anemia

	Anemic groups			Control group	P
	Group 1	Group 2	Group 3		
n	104	17	121	484	
Age (years)	26.6 ± 5.4*††	29.7 ± 5.9	28.8 ± 5.1	28.6 ± 4.8	0.001
Height (cm)	152.0 ± 5.9*	153.8 ± 7.1	152.9 ± 5.4	155.4 ± 5.3	<0.0001
Weight (kg)					
Prepregnancy	50.8 ± 9.5	52.3 ± 11.4	52.3 ± 8.7	51.9 ± 7.1	NS
Predelivery	60.5 ± 9.4*	62.9 ± 12.3	62.6 ± 9.6	65.0 ± 8.4	<0.0001
Increment	10.0 ± 4.5*	10.6 ± 6.1*	10.7 ± 4.1*	13.1 ± 4.4	<0.0001
BMI (kg/m ²)					
Prepregnancy	21.7 ± 2.6	21.9 ± 3.2	22.2 ± 2.6	21.5 ± 2.7	NS
Predelivery	26.1 ± 2.8	26.4 ± 3.9	26.7 ± 3.0	26.9 ± 3.2	NS
Increment	4.4 ± 2.0*	4.5 ± 2.7*	4.6 ± 1.8*	5.4 ± 1.8	<0.0001
MCV (fl) booking	82.1 ± 10.5*†	83.5 ± 11.6*	85.8 ± 6.4*	89.6 ± 3.9	<0.0001
Third trimester	79.4 ± 9.7*†	82.6 ± 13.5*	85.6 ± 8.0*	92.0 ± 8.4	<0.0001
Predelivery	81.1 ± 10.2*†	85.4 ± 12.7	84.5 ± 7.3*	88.8 ± 6.3	<0.0001

Data are means ± SD. Please refer to text for definition of anemic groups. MCV, mean cell volume. Analysis was performed by one-way ANOVA with post hoc analysis by Duncan's test: *P < 0.05 with control group; †P < 0.05 with group 2; ††P < 0.05 with group 3.

was subcategorized as follows: group 1, anemia at booking and third trimester; group 2, anemia before the third trimester; group 3, anemia only in the third trimester (Table 2). Whereas the significant differences in maternal age, height, and predelivery weight, which were largely accounted for by group 1, all three anemic subgroups accounted for the significant difference in weight and BMI increments among the anemic and control groups. There were significant differences in the MCV among all groups in the three measurements (Fig. 2). On further analysis, a significant inverse correlation was found between the prevalence of GDM with the severity and duration of anemia ($r = -0.074$, $P = 0.045$): 3.8% in group 1, 5.9% in group 2, 7.4% in group 3, and 9.8% in the control group (Fig. 3).

To determine the independent effect of anemia on the development of GDM, multiple logistic regression analysis was performed adjusting for parity and BMI, which showed a difference between the anemic and control groups. Anemia remained a significant factor associated with decreased prevalence of GDM (adjusted OR 0.46, 95% CI 0.23–0.90) after correcting for the effect of multiparity and BMI ≥ 25 kg/m².

CONCLUSIONS— In nonpregnant subjects, the association between high Hb concentration and red cell count with diabetes has been attributed to an increased proportion of glycosylated Hb in diabetic sub-

jects. It is generally regarded that the glycation of HbA does not affect oxygen transport. However, glycosylated Hb has increased oxygen affinity, and higher levels of glycosylated Hb could have led to sufficient tissue hypoxia, which stimulates an increase in Hb and red cell count (10, 19–21). Indeed, a correlation between reticulocyte count with glycemic control, paralleling the HbA_{1c} level, has been demonstrated in diabetic subjects after the exclusion of those with overt anemia and low serum iron concentration (21). Furthermore, increased iron stores in the general population have been associated with increased incidence of diabetes (22–24). These observations suggest that one prerequisite for the association between increased Hb and diabetes is the presence of at least an adequate, if not excessive, iron store in the individual.

Measurement of Hb concentration has become a standard investigation in pregnancy. Maternal Hb concentration reflects not only maternal nutritional status (16) but also the degree of hemodilution, both of which would impact pregnancy outcome as reflected by the relationship between high and low Hb concentration with adverse pregnancy outcome (1–6,16). In our population, the incidence of GDM was 10.9% in women with a booking Hb of between 10 and 11.5 g/dl, which was similar to that in the overall population (9). On the other hand, the incidence of GDM in women with anemia due to iron deficiency was

4.6%, compared with the 9.4% found in women with anemia due to thalassemia trait (15). Increased maternal ferritin concentration has been found at the time of diagnosis of GDM in the third trimester (25,26). It is therefore logical to hypothesize that women with iron deficiency anemia would have a reduced likelihood of GDM.

In this study, we have focused on women with iron deficiency anemia, and we demonstrated that iron deficiency anemia is independently associated with a reduced prevalence of GDM. Furthermore, the prevalence of GDM was related to the duration and timing of anemia. These women also had significantly decreased gestational increment in weight and BMI, which agreed with the finding that iron deficiency anemia diagnosed in early pregnancy was associated with low dietary energy and iron and inadequate gestational weight gain (16). Because our obstetric population is of the same ethnic background and culture, different dietary habits were unlikely to have played an important role in our findings, especially when vegetarians were excluded. In our anemic group, the nutritional deficiency had probably antedated pregnancy because although these patients were younger, they were shorter, which suggested poorer nutrition during childhood and adolescence. However, anemia in the third trimester is associated with less nutritional deficiency and lower impact on pregnancy outcome (16), and this would

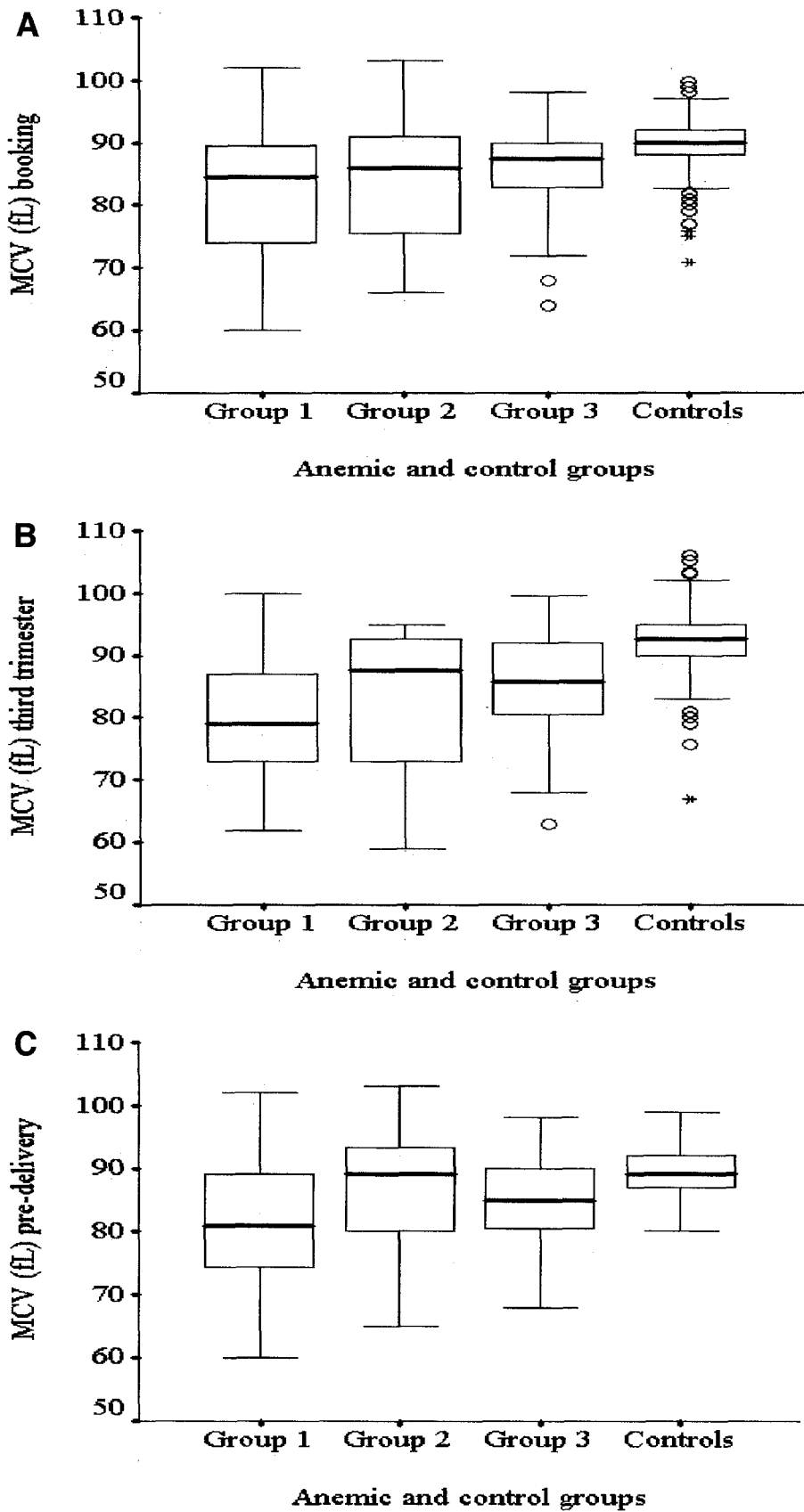


Figure 2—Box-whisker plots of maternal MCV values in the anemic and nonanemic control groups. A, B, and C: MCV values at booking, third trimester, and pre-delivery, respectively. Outlying values are circles. Extreme outlying values are asterisks. Comparison by one-way ANOVA; $P < 0.0001$ in all cases.

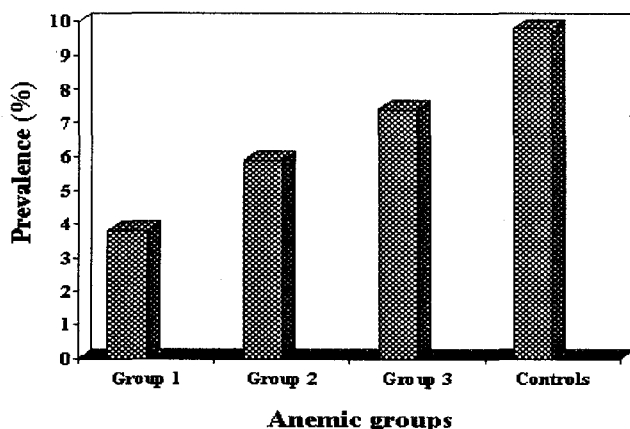


Figure 3—Prevalence of GDM in relation to duration and timing of iron deficiency anemia. See text for description of anemic groups. Comparison by Pearson's correlation between incidence of GDM and anemic groups; $P = 0.045$.

help explain the increasing prevalence of GDM from group 1 to group 3 in this study.

In our anemic women, MCV was significantly lower throughout pregnancy and was correlated with the duration and timing of anemia. Because MCV is a robust index of maternal iron status in women without hemoglobinopathies (17,18), our findings confirmed that the underlying etiology of the anemia was iron deficiency and not merely hemodilution. Taken together, our findings suggest that the decreased prevalence of GDM in women with iron deficiency anemia is likely to be consequent to the combined effects of iron deficiency, which also reflected nutritional deficiency in general and reduced gestational weight gain.

On the other hand, the anemic group had significantly increased incidence of LGA infants. In the literature, a significant inverse correlation between the lowest maternal Hb concentration in the second (5) and third (27) trimesters with birth weight were reported. In fact, maternal Hb concentration of 9.5 g/dl seemed optimal for fetal growth in all ethnic groups, and the maximum birth weight was found in women with the lowest Hb at 8.5–9.5 g/dl, whereas the lowest incidence of low birth weight was found in those with Hb of 9.5–10.5 g/dl (6). Our finding of increased incidence of LGA infants in all the anemic subgroups thus agreed with previous reports.

Our findings indicate that the likelihood of GDM is significantly reduced with maternal iron deficiency anemia, which probably acts also as a surrogate for

general nutritional deficiency. In the developing world, overall nutritional improvement and correction of anemia could be contributing factors to the increasing prevalence of diabetes and GDM (28,29). However, this should not be interpreted as evidence against iron supplementation for correction of maternal anemia, the importance of which is indisputable. Instead, it is the routine prescription of iron for nonanemic mothers that should be reappraised, because excess iron can affect insulin synthesis and secretion and enhance oxidation of lipids, which in turn decreases glucose utilization in muscles and increase gluconeogenesis in liver, thus leading to liver-mediated insulin resistance (30). Further studies on the role of nutritional factors in the development of diabetes and GDM are warranted, especially in developing countries.

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