The Journal of Nutrition
Nutritional Epidemiology

Plasma Concentrations of Ferritin in Early Pregnancy Are Associated with Risk of Gestational Diabetes Mellitus in Women in the Danish National Birth Cohort[1,2]

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Abstract

Background: Evidence from experimental studies has demonstrated that higher than normal iron concentrations can lead to pancreatic β cell dysfunction and impaired glucose metabolism. Studies on body iron stores in early pregnancy and subsequent gestational diabetes mellitus (GDM) risk are sparse.

Objective: Our objective was to determine whether biomarkers of body iron stores measured in early pregnancy are associated with GDM risk.

Methods: A case–control study of 350 GDM cases and 349 non-GDM controls was conducted in participants from the Danish National Birth Cohort. Blood was collected at a mean ± SD gestational age of 9.4 ± 3.2 wk. Plasma biomarkers of iron stores, including ferritin and soluble transferrin receptor (sTfR), were measured. Logistic regression was used to estimate the OR of GDM associated with quintiles of plasma biomarkers of body iron stores, controlling for maternal age, family history of diabetes, exercise in pregnancy, parity, and prepregnancy body mass index (BMI).

Results: Cases were older (mean ± SD age: 32.2 ± 4.3 compared with 29.9 ± 4.2 y) and had a higher BMI (in kg/m^2; mean ± SD: 28.7 ± 6.0 compared with 24.1 ± 4.6) than controls. Plasma concentrations of both ferritin and sTfR in early pregnancy were significantly higher in GDM cases than in controls [means ± SDs: 80.6 ± 56.0 compared with 71.8 ± 50.1 μg/L (P = 0.03) and 1.5 ± 0.7 compared with 1.4 ± 0.6 mg/L (P = 0.002) for ferritin and sTfR, respectively]. Ferritin was positively and significantly associated with GDM risk even after adjustment for major risk factors of GDM, including prepregnancy BMI. ORs across increasing quintiles of ferritin were 1.00 (reference), 1.25 (95% CI: 0.70, 2.22), 1.89 (95% CI: 1.06, 3.37), 0.82 (95% CI: 0.46, 1.48), and 2.34 (95% CI: 1.30, 4.21) (P–linear trend = 0.02).

Conclusion: These findings suggest that plasma ferritin measured in early pregnancy is significantly and positively associated with GDM risk. *J Nutr* 2016;146:1756–61.

Keywords: iron, biomarkers, pregnancy, gestational diabetes mellitus, plasma ferritin

Introduction

Gestational diabetes mellitus (GDM)[10] is a common pregnancy complication affecting between 7% and 14% of pregnancies in the United States (1) and ~2.4% of pregnancies in Denmark (2). Evidence from experimental studies demonstrated that iron overload, including from hereditary or secondary hemochromatosis (3), can induce β cell toxicity and impaired glucose metabolism (4). Although the exact molecular mechanism is not clear, iron is a strong pro-oxidant, and higher than normal iron concentrations may lead to diminished insulin secretion coupled withpregnancy-induced insulin resistance (5). Emerging findings from epidemiologic studies, although still limited, indicate that high dietary heme iron intake both before (6) and during (7) pregnancy and high total iron intake during pregnancy (8) were significantly related to an increased GDM risk.

[1] Supported by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, NIH (contract no. HHSN275201000020C), and NIH Office of Dietary Supplements.
[2] Author disclosures: KA Bowers, SF Olsen, W Bao, TI Halldorsson, M Strøm, and C Zhang, no conflicts of interest.
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[10] Abbreviations used: CRP, C-reactive protein; DNBC, Danish National Birth Cohort; GDM, gestational diabetes mellitus; ox-LDL, oxidized LDL; sTfR, soluble transferrin receptor.

Manuscript received February 3, 2016. Initial review completed March 10, 2016. Revision accepted July 6, 2016.
First published online August 10, 2016; doi:10.3945/jn.115.227793.

Although dietary studies are imperative and lay the foundation for future prevention studies, biomarkers of iron metabolism may provide additional important insights into the mechanism describing the association between dietary iron and GDM. Previous studies of biomarkers of body iron stores and GDM largely focused on ferritin, were of low sample size, and used cross-sectional or retrospective study designs (9–14). Prospective studies on the iron store biomarkers in early pregnancy are sparse. The objective of the current study, therefore, was to evaluate the risk of GDM in association with concentrations of body iron stores in early pregnancy, including ferritin and soluble transferrin receptor (sTfR), while taking into account systemic inflammation as measured by C-reactive protein (CRP) and oxidative stress as measured by oxidized LDL (ox-LDL).

Methods

The present study was nested within the Danish National Birth Cohort (DNBC). Details of the DNBC have been described extensively (15). Briefly, women were recruited in the first trimester of pregnancy between 1996 and 2002. Maternal computer-assisted telephone interviews were conducted at ~12 and 30 gestational weeks, as well as 6 and 18 mo postpartum, with follow-up of the offspring at ages 7 and 11 y. Blood was collected by general practitioners at 2 time points: 6–12 wk and 24–25 wk gestation. The early blood samples, at 6–12 wk, were used for biomarker measurement in the present study to evaluate body iron stores in early pregnancy. Women provided informed consent.

GDM case and control selection. The source population for the present study included 84,388 women who had a singleton pregnancy lasting ≥6 mo. Cases were selected from 1379 women who were suspected of having GDM. Women were suspected of having GDM if they did not experience prepregnancy diabetes, but either reported diabetes in pregnancy during telephone interviews, or had a GDM diagnosis recorded in the National Patient Registry for the index pregnancy. Hospital records were retrieved for all suspected GDM pregnancies, and information detailing oral glucose tests was extracted. Of those with suspected GDM, women were eligible for the present study if they had glucose test results on medical records and met WHO GDM diagnosis criteria (fasting glucose ≥7.0 mmol/L or 75-g oral-glucose-tolerance-test 2-h glucose ≥7.8 mmol/L). A total of 431 women met case eligibility criteria. A priori power calculations conducted for a nested case–control design assuming a 1:1 allocation of 350 cases and 350 controls and assuming a 0.05 α level (2-sided chi square test conducted at the 0.05 significance level) determined sufficient power to detect meaningful associations (OR = 2), even when the probability of exposure was small (<10%). Of the potential cases, 350 were randomly selected for inclusion in the present study. Controls were randomly selected from 2000 women randomly sampled from the DNBC who had a singleton pregnancy lasting ≥6 mo and for whom hospital records had been available from the index pregnancy and clearly indicated that they did not have GDM. Of these women, 349 controls were randomly selected.

Biomarker measurement. Blood for the present analyses was collected in EDTA-coated tubes during the first trimester (between 6 and 12 wk gestation). Blood was drawn in the nonfasting state and at various times of the day. Analyses described here were conducted on deidentified samples with the use of a study identification number. Blood samples were collected at general practitioner offices and sent by mail to Statens Serum Institute in Copenhagen, Denmark, where they were processed and stored in liquid nitrogen (16). Frozen samples were sent on dry ice from Denmark to the United States and remained frozen until biomarker analysis. Analyses were conducted at the Advanced Research and Diagnostic Laboratory at the University of Minnesota. Plasma ferritin, sTfR, and high-sensitivity CRP were measured with the use of an immunoturbidimetric assay on a Roche Modular P chemistry analyzer (Roche Diagnostics). ox-LDL concentrations were measured with the use of a Mercodia Oxidized LDL ELISA kit on a Beckman Coulter Biomek NXp Laboratory Automation Workstation. The interday coefficients of variability were as follows—oxLDL: 11.4% at 42.0 U/L; CRP: 2.1% at 5.28 mg/L; sTfR: 2.7% at 2.68 mg/L; and ferritin: 4.7% at 55.0 μg/L.

Covariates. Specific relevant covariates included family history of diabetes, smoking history during pregnancy, BMI, exercise habits in pregnancy, and details of previous pregnancies. These data were captured during the prenatal telephone interviews, which took place at ~12 and 30 gestational weeks.

Statistics. Means ± SDs for continuous baseline characteristics and proportions for categorical characteristics were compared between cases and controls. *t* Tests and chi-square tests were used to determine whether differences were statistically different. Biomarkers were assessed visually for normality and log-transformed as necessary. Multivariate logistic regression was used to estimate RR by generating ORs of GDM continuously and across quintiles of biomarkers. Models were adjusted for maternal age, prepregnancy BMI, family history of diabetes, ever exercise in pregnancy, and parity, as well as for CRP and ox-LDL, as appropriate. We used restricted cubic spline regressions to model the association between continuous ferritin and GDM. Potential effect modification by GDM risk factors across tertiles of biomarkers was assessed with the use of multiplicative interaction terms and the magnitude of heterogeneous effects estimated by stratification. GDM risk factors included BMI (in kg/m^2; <25 compared with ≥25), history of anemia, ever smoked during pregnancy, CRP [<2.14 (median) compared with ≥2.14 mg/L], family history of diabetes, and parity (nulliparous compared with parous). All statistical analyses were performed with SAS software.

Results

Baseline characteristics and potential risk factors for GDM in cases (n = 350) and non-GDM controls (n = 349) are presented in **Table 1**. Overall, women who had GDM in pregnancy were older, shorter, less educated, more likely to have a family history of diabetes and a higher prepregnancy weight and BMI, and less likely to be physically active and nulliparous. The mean gestational age of blood collection did not differ between cases and controls (9.4 compared with 9.3 gestational weeks). The mean plasma ferritin and sTfR concentrations were higher in cases than in controls (P = 0.03 and P = 0.002, respectively). In addition, GDM women had higher ox-LDL (P = 0.01) and CRP (P < 0.0001) concentrations than did controls in early pregnancy.

Plasma sTfR concentrations were significantly and positively associated with GDM risk even after the adjustment for family history of diabetes, ever exercise in pregnancy, and parity (**Table 2**). Overall the adjusted ORs increased across increasing quintiles of sTfR (P-trend: 0.002). However, the association was attenuated and became nonsignificant after the adjustment for prepregnancy BMI (P-trend: 0.37). Additional adjustment for CRP and ox-LDL did not significantly affect the ORs.

Plasma ferritin concentrations were significantly and positively associated with GDM risk (Table 2). After adjustment for major risk factors of GDM, including prepregnancy BMI, the ORs comparing the highest with the lowest quintiles of ferritin demonstrated a >2-fold increased odds of GDM with P–linear trend = 0.02 across quintiles. The association was attenuated slightly but remained significant after additional adjustment for CRP and ox-LDL. The continuous association between ferritin and GDM is also detailed in Table 2 and can be visualized in **Figure 1**.

The associations between plasma ferritin and GDM persisted across subgroups as defined by risk factors of GDM, including BMI, history of anemia, CRP, and family history of diabetes (P-interaction = 0.61, 0.81, 0.86, and 0.35, respectively).

TABLE 1 Baseline characteristics comparing 350 women with GDM with 349 women without GDM, nested within the Danish National Birth Cohort[1]

	Cases (n = 350)	Controls (n = 349)	P
Age at birth, y	32.2 ± 4.3	29.9 ± 4.2	<0.0001
Socioeconomic status (highest-level professional)[2]	60 (18.1)	78 (22.5)	0.10
Graduated high school	100 (38.1)	124 (53.0)	0.003
Cohabitation status (pairs)	329 (99.1)	345 (98.9)	0.75
Family history of diabetes	97 (28.0)	28 (8.0)	<0.0001
History of metabolic disorders	11 (3.3)	4 (1.2)	0.05
History of anemia	52 (15.6)	53 (15.2)	0.99
Iron-deficient anemia	20 (6.0)	15 (4.3)	0.54
Height, cm	167.1 ± 6.0	168.7 ± 6.3	0.001
Prepregnancy weight, kg	80.1 ± 17.8	68.4 ± 13.8	<0.0001
Prepregnancy BMI, kg/m^2	28.7 ± 6.0	24.1 ± 4.6	<0.0001
Prepregnancy BMI by category, kg/m^2			<0.0001
≤18.5	2 (0.6)	9 (2.6)	
>18.5 to <25	98 (30.3)	220 (64.5)	
≥25 to <30	103 (31.9)	73 (21.4)	
≥30 to <35	77 (23.8)	26 (7.6)	
≥35 to <40	31 (9.6)	10 (2.9)	
≥40	12 (3.7)	3 (0.9)	
Anemia (ever)	52 (14.9)	53 (15.2)	0.90
Nonsmoker	242 (70.1)	265 (75.9)	0.38
Any exercise during pregnancy	100 (30.0)	141 (40.4)	0.005
Gravidity (0)	85 (25.5)	143 (41.1)	0.0002
Primiparity	128 (37.9)	175 (51.6)	0.02
Plasma biomarkers in early pregnancy			
sTfR, mg/L	1.5 ± 0.7	1.4 ± 0.6	0.002
Ferritin, μg/L	80.6 ± 56.0	71.8 ± 50.1	0.03
Ferritin:sTfR ratio	67.4 ± 77.3	64.1 ± 69.5	0.55
ox-LDL, U/L	24.8 ± 6.80	23.4 ± 7.9	0.01
CRP, mg/L	6.5 ± 6.7	3.7 ± 5.3	<0.0001

[1] Continuous variables are expressed as means ± SDs and categorical data are expressed as n (%). Percentage missing for cases compared with controls: education level, 27% compared with 33%; family history of diabetes, 34% compared with 46%; anemia late in pregnancy, 11% compared with 10%; and anemia in the last weeks of pregnancy, 22% compared with 26%. CRP, C-reactive protein; GDM, gestational diabetes mellitus; ox-LDL, oxidized LDL; sTfR, soluble transferrin receptor.

[2] Socioeconomic status was defined by Statistics Denmark (17). The category ''highest-level professional'' included management at the highest levels in corporations, companies, organizations, and the public sector, or work that requires skills at the highest level for each discipline.

The associations, however, differed significantly by cigarette smoking status during pregnancy (P-interaction = 0.03) and nulliparity status (P-interaction = 0.003). Among ever smokers, the OR comparing extreme tertiles of plasma ferritin concentration was ~2-fold, whereas for never smokers it was null. For parous women, the OR comparing extreme tertiles of plasma ferritin concentration demonstrated a 1.5-fold increased odds, with a significant P-trend across tertiles (P = 0.01). However, for nulliparous women, the OR comparing extreme tertiles was null and across tertiles there was not a significant trend (P = 0.30).

Discussion

In this prospective nested case–control study of pregnant women, plasma ferritin concentrations in early pregnancy were significantly and positively associated with GDM risk even after adjustment for prepregnancy BMI and additional GDM risk factors. The association remained significant after adjustment for markers of systematic inflammation and oxidative stress. The association appeared to be stronger in smokers and parous women than in their nonsmoking and nulliparous counterparts.

Studies on body iron stores in early pregnancy and GDM risk are sparse. We are aware of only one prospective study that included a small number of GDM cases (n = 35). Our findings, which used plasma samples collected at 9 wk gestation on average, are consistent with this study, which showed a statistically significant and >2-fold increased risk of developing GDM for women in the highest compared with the lowest quintile of plasma ferritin measured at ~15 gestational weeks (11). The majority of other previous studies are retrospective and/or cross-sectional (9, 10, 12, 18). Our findings are in general in line with findings from prospective studies in nonpregnant individuals on iron store and type 2 diabetes mellitus. For instance, a study nested within the Nurses' Health Study identified an adjusted RR for type 2 diabetes of 2.68 (1.75, 4.11) when comparing extreme quintiles of plasma ferritin concentration (highest compared with the lowest) (19).

The observed association between plasma ferritin and GDM risk is biologically plausible. Iron overload consistently has been associated with risk of both type 2 diabetes (19) and GDM (9). The exact mechanism by which excess iron contributes to diabetes has not been fully revealed; however, iron is a redox-active transitional metal that is a powerful pro-oxidant. It is

TABLE 2 Associations of plasma sTfR and ferritin concentrations with gestational diabetes mellitus risk in 350 cases and 349 controls nested within the Danish National Birth Cohort[1]

Quintiles of biomarkers (median)	Cases, *n*	OR (95% CI)[2]	OR (95% CI)[3]	OR (95% CI)[4]	OR (95% CI)[5]
sTfR, mg/L					
1 (0.79)	57	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
2 (1.08)	73	1.36 (0.84, 2.22)	1.47 (0.88, 2.45)	1.80 (1.02, 3.19)	1.82 (1.02, 3.22)
3 (1.34)	62	1.17 (0.71, 1.92)	1.36 (0.81, 2.28)	1.30 (0.73, 2.31)	1.33 (0.75, 2.37)
4 (1.65)	76	1.79 (1.09, 2.94)	1.97 (1.18, 3.30)	1.53 (0.87, 2.71)	1.63 (0.92, 2.89)
5 (2.26)	82	2.10 (1.10, 1.18)	2.13 (1.27, 2.59)	1.50 (0.83, 2.70)	1.48 (0.82, 2.70)
P-trend		0.002	0.003	0.37	0.36
Per-unit increment		1.53 (1.19, 1.96)	1.53 (1.19, 1.98)	1.21 (0.91, 1.61)	1.21 (0.90, 1.63)
Ferritin, μg/L					
1 (25.0)	60	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
2 (45.0)	71	1.46 (0.89, 2.39)	1.47 (0.87, 2.46)	1.25 (0.70, 2.22)	1.17 (0.65, 2.11)
3 (66.0)	75	1.56 (0.95, 2.55)	1.74 (1.04, 2.91)	1.89 (1.06, 3.37)	1.84 (1.03, 3.28)
4 (87.0)	55	0.90 (0.55, 1.47)	0.93 (0.56, 1.57)	0.82 (0.46, 1.48)	0.77 (0.43, 1.40)
5 (141.0)	89	2.33 (1.41, 3.84)	2.63 (1.56, 4.44)	2.34 (1.30, 4.21)	2.22 (1.23, 4.01)
P-trend		0.008	0.003	0.02	0.03
Per–10-unit increment		1.03 (1.00, 1.06)	1.04 (1.00, 107)	1.03 (1.00, 1.06)	1.03 (1.00, 1.06)

[1] Ref, reference; sTfR, soluble transferrin receptor.
[2] Adjusted for age.
[3] Adjusted for age, family history of diabetes, ever exercise in pregnancy, and parity (only in sTfR models).
[4] Adjusted for age, family history of diabetes, ever exercise in pregnancy, parity (only in sTfR models), and prepregnancy BMI.
[5] Adjusted for age, family history of diabetes, ever exercise in pregnancy, parity (only in sTfR models), prepregnancy BMI, C-reactive protein, and oxidized LDL.

believed that iron-dependent Fenton reactions produce reactive oxygen species (including hydroxyl radicals) capable of disrupting insulin signaling in the liver and skeletal muscle tissue while also damaging pancreatic β cells (20). Given minimal endogenous antioxidant defenses, the pancreatic β cell is especially susceptible to oxidative damage (5). In addition, little iron is excreted from the body, leading to a potential for iron surplus because of dietary and supplemental intake (5). In our previous analysis of dietary and supplemental iron intake, we identified an association between heme iron intake and GDM (6). In a prospective study of 13,475 women (including 867 incident GDM cases) consumption of the highest quintile of heme iron was significantly and positively associated with GDM (OR = 1.58; 95% CI: 1.21, 2.08). Taken together with the present findings, we have provided stronger evidence for the role of iron on the risk of GDM. In addition, the stronger association between plasma ferritin and GDM in smokers is consistent with our previous findings on dietary iron and GDM. We previously identified an increased risk of GDM from prepregnancy (6) and pregnancy (7) dietary heme iron intake in smokers. Cigarette smoke contains multiple oxidants that may exacerbate the pro-oxidant effect of iron (6). Similarly, in the present analyses, the association between plasma ferritin and GDM was appreciably stronger in ever smokers in pregnancy compared with never smokers in pregnancy. The finding of a stronger association between plasma ferritin and GDM in parous women was not observed previously and warrants confirmation in future studies. In our analyses, we observed only a minor reduction in the association between plasma ferritin and GDM after controlling for ox-LDL; however, this is not surprising, given the low correlation between the 2 biomarkers in this dataset (r^2 = 0.002, P = 0.96, data not shown). Our study findings suggest that, at most, there is a modest role of ox-LDL in the association between plasma ferritin and GDM, despite our a priori hypothesis regarding the role of oxidative stress. However, this does not rule out oxidative stress as a mediating mechanism. Although quantifying ox-LDL is a widely used indirect method for measuring oxidative stress, it does not represent all oxidative stress pathways. Future studies warrant investigation of additional oxidative stress pathways.

Because internal body metabolic and physiologic conditions can influence body iron stores significantly, and in order to evaluate overall body iron load, we measured plasma ferritin and sTfR concentrations as opposed to measures of supplement intake. Ferritin concentrations are regarded as the best single measure of iron stores. However, a potential concern about the use of ferritin concentrations as a measure of body iron stores is that ferritin also increases with increased systemic inflammation. Particularly relevant to the current analyses is inflammation from preclinical diabetes, obesity, and/or the inflammation inherent in pregnancy. We attempted to minimize potential

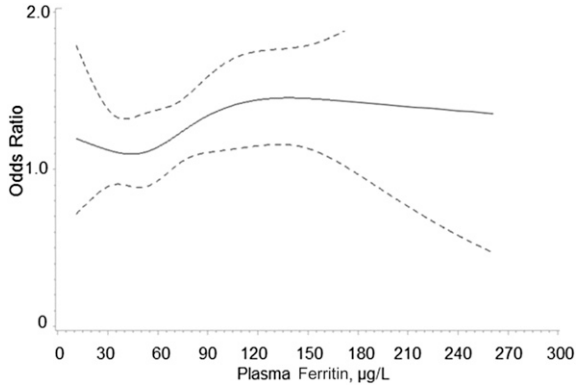

FIGURE 1 ORs and 95% CIs describing the association between plasma ferritin and gestational diabetes mellitus risk in n = 350 cases and n = 349 controls within the Danish National Birth Cohort.

confounding from these factors by controlling for CRP, a measure of systemic inflammation, and for prepregnancy BMI in multivariate models. Although levels of inflammation change throughout pregnancy, the timing of the blood draw during pregnancy was statistically indistinguishable when comparing cases with controls, with a mean ± SD of 65.9 ± 22.9 and 65.2 ± 22.6 d, respectively ($P = 0.73$).

The concentration of sTfR is also an indicator of iron status, because iron deficiency leads to an overexpression of sTfR concentrations, whereas sTfR is decreased in the presence of iron overload (21). We measured plasma sTfR in addition to plasma ferritin, because it may be a useful biomarker in cases in which ferritin is elevated because of conditions such as inflammation and infection (22). Indeed, the OR describing the association between sTfR and GDM was not affected appreciably by adjustment for CRP. However, interpretation of the sTfR and GDM relation is complex. After adjustment for prepregnancy BMI, sTfR was not associated with GDM risk. These results were consistent with previous studies that indicate that sTfR is positively associated with obesity (23). Whether sTfR meaningfully captures the association between higher iron concentrations and GDM is currently unclear, but worthy of further investigation.

The prevalence of GDM (2.6%) in this study was relatively low. However, it fell within the reported prevalence range of those in the Northern and Atlantic seaboard areas of Europe (mostly <4%) (2), and it is consistent with the reported prevalence in a prospective multiple center study in Denmark (2.7%) (24). Future studies in other populations are warranted to confirm the findings. It also should be noted that a majority of the controls did not have fasting glucose concentration or glucose tolerance tests. Although the possibility cannot be excluded that in our controls there may have been GDM cases, given the free-of-charge and relatively intensive health examination program during pregnancy in Denmark, this would be very unlikely. Finally, biospecimen sampling did not occur at a standardized time of day. Although iron markers can demonstrate diurnal variation, there is no indication that the cases and controls varied in blood collection time distributions; therefore, differential bias was unlikely.

There are several unique strengths of the current study, including the prospective study design and large sample size nested in a well-characterized pregnancy cohort, the Danish National Birth Cohort. We included 350 cases of GDM and 349 controls, which is a substantial increase in cases from previous studies, and hospital records had been carefully reviewed for all case and control pregnancies. In addition, the blood samples were collected very early in pregnancy (at ~9 gestational weeks) and before the onset of GDM. With the exception of one small prospective study (11), previous studies have measured ferritin at the time of GDM diagnosis or later. In the present study, we were able to investigate the relation between markers of iron stores and markers of inflammation before the onset of GDM. Finally, we adjusted for both CRP and additional covariates to reduce the possibility of confounding.

In summary, findings from this study suggest that higher concentrations of plasma ferritin in early pregnancy are significantly and positively associated with the development of GDM. Further clinical studies are warranted to determine whether modifying iron intake and/or other methods to reduce iron stores may provide a pathway for prevention of some cases of GDM. In addition, further work is necessary to understand the underlying mechanisms.

Acknowledgments

KAB contributed to the study design, conducted the analyses, and drafted the manuscript; SFO contributed to the study design and interpretation of the data and reviewed and edited the manuscript; WB and CZ contributed to the study design, data analyses, and interpretation of the data, and reviewed and edited the manuscript; TIH and MS contributed to the interpretation of the data and reviewed and edited the manuscript; and KAB and CZ are the guarantors of this work. All authors read and approved the final manuscript.

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