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Original Research

Serum Ferritin and Glucose Homeostasis in Women With Recent Gestational Diabetes

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Key Messages

- Serum ferritin does not differ between women with recent gestational diabetes and their peers at 1 or 3 years postpartum.
- Ferritin is not independently associated with insulin sensitivity, beta-cell function, glycemia or glucose tolerance within this window.
- Serum ferritin is not associated with glucose homeostasis in the early years after a gestational diabetes pregnancy.

A R T I C L E I N F O

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A B S T R A C T

Objectives: Serum markers of iron storage have been linked to type 2 diabetes; however, the mechanism underlying this association is unclear. In pregnancy, increased serum ferritin has been reported in women with gestational diabetes (GDM), a patient population at high risk of future type 2 diabetes. However, in the years after pregnancy, it is not known if ferritin relates to their diabetes risk or the pathophysiologic determinants thereof (insulin sensitivity and beta-cell function). Therefore, we sought to characterize the relationship between ferritin and glucose homeostasis in the early postpartum years in women with and without recent GDM.
Methods: At both 1 and 3 years postpartum, 340 women (105 with recent GDM) underwent serum ferritin measurement and an oral glucose tolerance test that enabled assessment of insulin sensitivity and/or resistance (Matsuda index and Homeostasis Model Assessment [HOMA-IR]), beta-cell function (Insulin Secretion-Sensitivity Index-2 and insulinogenic index/HOMA-IR) and glucose tolerance.
Results: Serum ferritin did not differ between women who had GDM and their peers at either 1 or 3 years postpartum. Baseline-adjusted change in ferritin between 1 and 3 years correlated with the concomitant change in C-reactive protein (r=0.21, p=0.0002) but was not associated with measures of insulin sensitivity and/or resistance, beta-cell function or glycemia. On adjusted analyses, neither baseline ferritin nor its change from 1 to 3 years was independently associated with any of the following metabolic outcomes at 3-years postpartum: Matsuda index, HOMA-IR, Insulin Secretion-Sensitivity Index-2, insulinogenic index/HOMA-IR, fasting glucose, 2-h glucose or glucose intolerance.
Conclusions: Serum ferritin is not associated with glucose homeostasis in the early years after a GDM pregnancy.

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RÉSUMÉ

Objectifs : Les marqueurs sériques du stockage du fer ont été associés au diabète de type 2. Toutefois, on ignore le mécanisme sous-jacent à cette association. Durant la grossesse, on a signalé des concentrations sériques accrues de la ferritine chez les femmes atteintes du diabète sucré gestationnel (DSG), une population de patientes exposées à un risque élevé d'un futur diabète de type 2. Toutefois, dans les années qui suivent la grossesse de ces femmes, on ignore si la ferritine a un lien avec leur risque de diabète ou les déterminants physiopathologiques de ce dernier (insulinosensibilité et fonctionnement des cellules bêta). Par conséquent, nous avons cherché à décrire la relation entre la ferritine et l'homéostasie glucidique dans les premières années qui suivent l'accouchement des femmes atteintes ou non d'un DSG récent.
Méthodes : Un an et 3 ans après l'accouchement, 340 femmes (dont 105 étaient atteintes d'un DSG récent) ont subi des analyses pour mesurer les concentrations sériques de la ferritine et une épreuve d'hyperglycémie provoquée par voie orale qui a permis l'évaluation de l'insulinosensibilité et/ou de l'insulinorésistance (indice de Matsuda et l'évaluation du modèle d'homéostasie de l'insulinorésistance [de l'anglais, HOMA-IR]), le fonctionnement des cellules bêta (indice d'insulinosécrétion et d'insulinosensibilité 2 [de l'anglais, ISSI-2] et l'indice insulinogénique/HOMA-IR) et la tolérance au glucose.
Résultats : Les concentrations sériques de la ferritine n'étaient pas différentes entre les femmes qui avaient un DSG et leurs pairs 1 an ou 3 ans après l'accouchement. Les changements ajustés aux concentrations initiales de la ferritine entre 1 et 3 ans étaient en corrélation avec les changements concomitants de la protéine C réactive ($r = 0{,}21$, $p = 0{,}0002$), mais n'étaient pas associés aux mesures de l'insulinosensibilité et/ou de l'insulinorésistance, au fonctionnement des cellules bêta ou à la glycémie. Dans les analyses ajustées, ni les concentrations initiales de la ferritine ni leurs changements après 1 et 3 ans n'étaient indépendamment associés aux résultats métaboliques suivants 3 ans après l'accouchement: indice de Matsuda, HOMA-IR, indice ISSI-2, indice insulinogénique/HOMA-IR, glycémie à jeun, 2 heures après avoir bu un liquide contenant 75 g de glucose ou intolérance au glucose.
Conclusions : Les concentrations sériques de la ferritine ne sont pas associées à l'homéostasie glucidique dans les premières années après la grossesse des femmes atteintes d'un DSG.

Introduction

It has long been known that gross iron overload, as occurs in hemochromatosis, is associated with an increased risk of diabetes (1,2). In the past 2 decades, a growing body of evidence has suggested that even mildly elevated iron stores may be linked to type 2 diabetes (T2DM). Indeed, in epidemiologic studies, surrogate markers of iron storage (particularly increased serum ferritin) predict the development of T2DM (3–6). However, the pathophysiologic basis underlying this relationship remains unclear. Moreover, the potential confounding effect of subclinical inflammation, which can increase serum ferritin and is itself associated with T2DM, has been queried in this setting (2).

Gestational diabetes mellitus (GDM) shares pathophysiologic similarities with T2DM in that both conditions are characterized by chronic insulin resistance and beta-cell dysfunction (7,8). Similarly, several studies report that increased serum ferritin in early pregnancy can predict the subsequent development of GDM (9–13). In the years after pregnancy, women who had GDM are at high risk of progressing to T2DM because of ongoing worsening of beta-cell function that is exacerbated by insulin resistance (7,8). However, it is not known if ferritin relates to a woman's risk of developing T2DM in this setting or to the pathophysiologic determinants thereof (insulin sensitivity and beta-cell function). Therefore, in this study, we sought to characterize the relationship between ferritin and glucose homeostasis in the early postpartum years in women with and without recent GDM.

Methods

The study population was composed of women participating in a prospective observational cohort study to investigate the relationship between gestational glucose tolerance and metabolic function in the years after delivery. The study protocol has been previously described in detail (7). Briefly, women were recruited in the second to third trimester of pregnancy at the time of antepartum GDM screening. They then returned to clinical research unit for assessment at 3 months and 1 year postpartum. At the latter visit, participants were recruited to participate in a long-term cohort study where serial cardiometabolic measurements are performed biannually thereafter. The 103 women who declined to participate in the long-term cohort did not differ from the 340 women who participated in the current analysis with respect to age, ethnicity, family history of diabetes and glucose tolerance (data not shown). The study protocol was approved by the Mount Sinai Hospital Research Ethics Board, and all participants provided written informed consent. This study is reported according to the STrengthening the Reporting of OBservational studies in Epidemiology guidelines (https://strobe-statement.org/index.php?id=strobe-home).

Recruitment and assessment in pregnancy

All pregnant women at our centre were screened for GDM between 24 and 28 weeks' gestation with a 50-g glucose challenge test (GCT). If the GCT was abnormal (defined as plasma glucose ≥7.8 mmol/L at 1 h after ingestion of 50 g glucose), a diagnostic oral glucose tolerance test (OGTT) was performed. For this study, women were recruited either before or after the screening GCT, and all women subsequently underwent a 3-h 100-g OGTT for determination of gestational glucose tolerance status, regardless of their GCT result. As previously described (7), the recruitment of women after an abnormal GCT served to enrich the study population for those with GDM. For the current analysis, the study population was stratified into those who had GDM and those who did not have GDM (control group). GDM was defined by the National Diabetes Data

Group criteria (14), which require at least 2 of the following on the OGTT: fasting blood glucose ≥5.8 mmol/L, 1-h glucose ≥10.6 mmol/L, 2-h glucose ≥9.2 mmol/L or 3-h glucose ≥8.1 mmol/L.

Assessments at 1 and 3 years postpartum

At both 1 and 3 years postpartum, the participants were reassessed at the clinical research unit after overnight fast and underwent a 2-h 75-g OGTT, on which glucose tolerance status was defined according to the current Diabetes Canada clinical practice guidelines (15). On each OGTT, venous blood samples were drawn for measurement of glucose and specific insulin at fasting and 30, 60 and 120 min after ingestion of the glucose load. Specific insulin was measured with the Roche-Elecsys-1010 immunoassay analyzer and electrochemiluminescence immunoassay kit (Roche Diagnostics, Laval, Quebec, Canada). Whole-body insulin sensitivity was assessed by the Matsuda index (16), and insulin resistance (primarily hepatic) was measured by the Homeostasis Model Assessment (HOMA-IR) (17). Beta-cell function was assessed with the Insulin Secretion-Sensitivity Index-2 (ISSI-2), a validated measure of beta-cell compensation that is analogous to the disposition index obtained from the intravenous glucose tolerance test against which it has been directly validated (18,19). Insulinogenic index (IGI)/HOMA-IR provided a second established measure of beta-cell function (7).

At each of these visits, serum ferritin was measured by Roche Modular electrochemiluminescence immunoassay (Roche Diagnostics). High-sensitivity C-reactive protein (CRP) was measured by endpoint nephelometry using the Dade-Behring BN ProSpec and N high-sensitivity CRP reagent (Dade-Behring, Mississauga, Ontario, Canada) to provide a measure of subclinical inflammation.

Outcomes of interest and potential confounders

The primary outcomes of interest were the following metabolic outcomes at 3 years postpartum: Matsuda index, HOMA-IR, ISSI-2, IGI/HOMA-IR, fasting glucose and 2-h glucose. Potential confounders included the following diabetes risk factors: age, ethnicity, family history of diabetes, body mass index (BMI) and duration of breastfeeding. The fully adjusted models were, therefore, adjusted for these variables.

Statistical analyses

All analyses were conducted using SAS 9.4 (SAS Institute, Cary, North Carolina, United States). All tests were 2-sided and performed at significance level $p<0.05$. Continuous variables were tested for normality of distribution. Variables with normal distributions are presented as mean ± SD, and those with skewed distributions are presented as median and interquartile range (25th to 75th percentile). Characteristics of the women who had GDM and those who did not have GDM were compared at 1 and 3 years postpartum by either 1-way analysis of variance for continuous variables (if normally distributed) or Kruskal-Wallis test for continuous variables (if skewed), and either chi-square or Fisher exact test for categorical variables (Table 1). Mean adjusted levels of serum ferritin at 1 and 3 years postpartum were compared between women with and without recent GDM and between women with and without current prediabetes or diabetes. Ferritin levels were adjusted for age, ethnicity, family history of diabetes, current BMI, duration of breastfeeding in first year and either current glucose tolerance status (Figure 1, plot i of each panel) or GDM status in pregnancy (Figure 1, plot ii of each panel). Spearman correlation analyses were conducted to evaluate the associations of 1) ferritin at 1 year postpartum, 2) ferritin at 3 years postpartum and 3) baseline-adjusted change in ferritin between 1 and 3 years postpartum, with baseline-adjusted changes in metabolic factors between 1 and 3 years postpartum. Multiple linear regression analyses were performed to determine whether ferritin at 1 year postpartum or the change in ferritin between 1 and 3 years postpartum was an independent predictor of the following metabolic outcomes at 3 years: Matsuda index, HOMA-IR, ISSI-2, IGI/HOMA-IR, fasting glucose and 2-h glucose. Each model was adjusted for the following covariates: 1) diabetes risk factors (age, ethnicity, family history of diabetes, duration of breastfeeding, BMI at 1 year and change in BMI from 1 to 3 years), 2) the measure of the respective outcome variable at 1 year postpartum and 3) both CRP and ferritin at 1 year and the respective changes in CRP and ferritin from 1 to 3 years. The inclusion of CRP enabled adjustment for a measure of subclinical inflammation. Finally, forward selection

Table 1
Comparison of demographic, clinical and metabolic characteristics at 1 and 3 years postpartum between women who had GDM and those who did not have GDM

Characteristics	Non-GDM (n=235)	GDM (n=105)	p value
1 year postpartum			
Age, years	36±4	36±4	0.36
Ethnicity			0.16
White	170 (72.3)	69 (65.8)	
Asian	23 (9.8)	18 (17.1)	
Other	42 (17.9)	17 (17.1)	
Family history of T2DM	137 (58.3)	68 (64.8)	0.26
Breastfeeding, months	10 (5.5–12.0)	10 (3.0–12.0)	0.55
Current smoking	10 (4.3)	2 (2.0)	0.36
BMI, kg/m^2	24.4 (21.8–28.7)	25.4 (22.5–29.4)	0.36
Matsuda index	10.2 (5.5–14.5)	7.6 (4.4–11.0)	0.0006
HOMA-IR	1.1 (0.7–1.8)	1.2 (0.7–2.0)	0.27
ISSI-2	806.2±303.9	669.9±268.0	0.0002
Insulinogenic index/HOMA-IR	10.3 (6.4–16.5)	7.1 (4.4–12.1)	0.0001
OGTT			
Fasting glucose, mmol/L	4.7±0.5	4.9±0.5	0.002
2-h glucose, mmol/L	5.9±1.6	7.0±1.9	<0.0001
Current glucose tolerance status			<0.0001
Normal	195 (87.8)	69 (69.7)	
Prediabetes and/or diabetes	27 (12.2)	30 (30.3)	
CRP, mg/L	1.1 (0.6–3.2)	1.1 (0.7–3.1)	0.74
Ferritin, μg/L	43.0 (29.0–60.0)	46.0 (32.0–66.0)	0.17
3 years postpartum			
Current smoking	14 (6.1)	3 (2.9)	0.29
BMI, kg/m^2	24.6 (21.9–28.9)	25.4 (22.3–30.1)	0.19
Matsuda index	8.7 (5.4–11.8)	6.3 (4.1–9.7)	0.0004
HOMA-IR	1.2 (0.8–1.9)	1.4 (1.0–2.4)	0.01
ISSI-2	868.7±364.3	667.8±363.2	<0.0001
Insulinogenic index/HOMA-IR	11.2 (7.2–18.7)	6.7 (4.4–11.2)	<0.0001
OGTT			
Fasting glucose, mmol/L	4.6±0.5	4.9±0.6	<0.0001
2-h glucose, mmol/L	6.0±1.7	7.4±2.2	<0.0001
Current glucose tolerance status			<0.0001
Normal	204 (86.8)	67 (63.8)	
Prediabetes and/or diabetes	31 (13.2)	38 (36.2)	
CRP, mg/L	1.0 (0.4–2.3)	1.5 (0.6–3.0)	0.02
Change in CRP from 1 year	−0.03±4.8	0.24±4.0	0.62
Ferritin, μg/L	38.0 (22.0–57.0)	43 (24.0–61.0)	0.26
Change in ferritin from 1 year	−4.4±24.4	−9.0±41.9	0.22

BMI, body mass index; *CRP,* C-reactive protein; *GDM,* gestational diabetes; *HOMA-IR,* Homeostasis Model Assessment; *ISSI-2,* Insulin Secretion-Sensitivity Index-2; *OGTT,* oral glucose tolerance test; *T2DM,* type 2 diabetes.
Note: Values are shown as mean ± SD (if normally distributed) or median (interquartile range) (if skewed) for continuous variables, n (%) or as otherwise indicated.

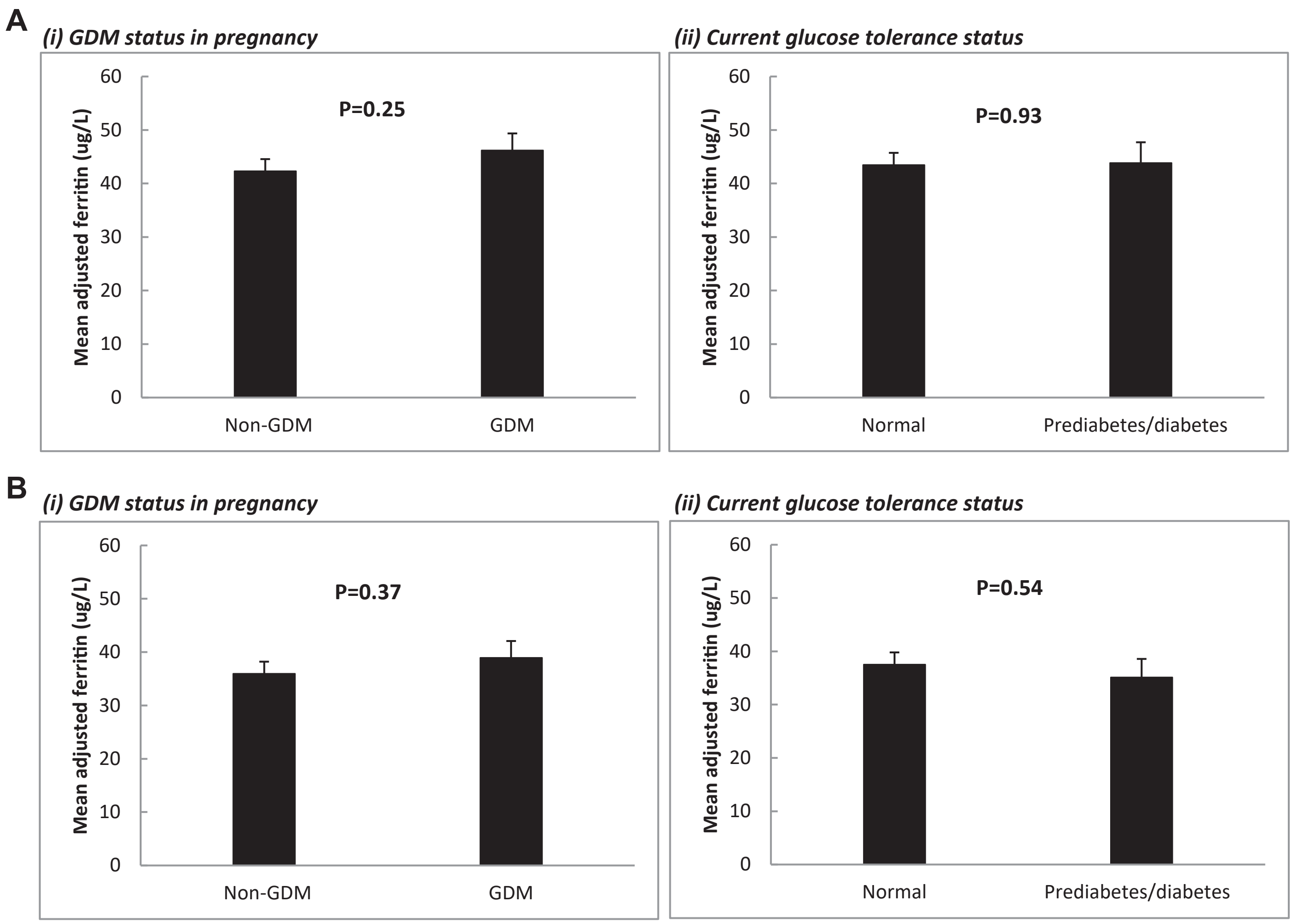

Figure 1. Comparison of mean adjusted levels of ferritin at (A) 1 year postpartum and (B) 3 years postpartum between women with and without recent GDM (plot i in each panel) and between women with and without current prediabetes and/or diabetes (plot ii in each panel). All values are adjusted for age, ethnicity, family history of diabetes, current body mass index, duration of breastfeeding in first year and either current glucose tolerance status (in plot i of each panel) or GDM status in recent pregnancy (in plot ii of each panel). *GDM*, gestational diabetes.

logistic regression analysis was performed to identify independent predictors of prediabetes and/or diabetes at 3 years postpartum. The covariates included in this analysis were the same as those in the multiple linear regression models.

Results

Comparison of ferritin between women with and without recent GDM

Table 1 shows the demographic, clinical and metabolic characteristics of the study population at both 1 and 3 years postpartum, stratified into those who did not have recent GDM (n=235) and those who did have GDM (n=105). The 2 groups did not differ in age, ethnicity, family history of T2DM, BMI or duration of breastfeeding at 1 year postpartum. As anticipated, at 1 year, women with recent GDM had lower whole-body insulin sensitivity (Matsuda index: $p=0.0006$), poorer beta-cell function (ISSI-2: $p=0.0002$; IGI/HOMA-IR: $p=0.0001$) and greater glycemia (fasting glucose: $p=0.002$; 2-h glucose: $p<0.0001$) than the non-GDM group, coupled with a higher prevalence of prediabetes and/or diabetes ($p<0.0001$). However, neither CRP nor ferritin differed between the non-GDM and GDM groups (ferritin: median, 43.0 vs 46.0 μg/mL, respectively; $p=0.17$).

At 3 years postpartum, the non-GDM and GDM groups continued to differ with respect to insulin sensitivity, beta-cell function, fasting glucose, 2-h glucose and current glucose tolerance (Table 1). CRP was now higher in the GDM group ($p=0.02$). However, neither serum ferritin nor the change in ferritin between 1 and 3 years differed between the GDM and non-GDM groups.

We next sought to determine whether either recent GDM or current glucose tolerance was independently associated with ferritin at 1 and 3 years postpartum (Figure 1). After adjustment for diabetes risk factors (age, ethnicity, family history of diabetes, current BMI and duration of breastfeeding) and current glucose tolerance status, there was no significant difference in mean adjusted ferritin between the GDM and non-GDM groups at either 1 year (Figure 1A, plot i) or 3 years (Figure 1B, plot i). Similarly, after adjustment for the same diabetes risk factors and GDM status, there was no difference in mean adjusted ferritin between women with and without current prediabetes and/or diabetes at either 1 year (Figure 1A, plot ii) or 3 years (Figure 1B, plot ii).

Associations of ferritin with metabolic factors

On Spearman correlation analysis, ferritin at 1 and 3 years showed no associations with baseline-adjusted changes between 1 and 3 years in BMI, insulin sensitivity and/or resistance, beta-cell

Table 2
Spearman correlations of ferritin at 1 year postpartum, ferritin at 3 years postpartum and baseline-adjusted change in ferritin between 1 and 3 years postpartum, with baseline-adjusted changes in metabolic factors between 1 and 3 years postpartum

Baseline-adjusted changes between 1 and 3 years	Ferritin at 1 year		Ferritin at 3 years		Baseline-adjusted change in ferritin between 1 and 3 years	
	r value	p value	*r* value	p value	*r* value	p value
BMI	−0.03	0.60	−0.07	0.18	−0.004	0.94
Matsuda index	−0.05	0.36	−0.06	0.32	−0.02	0.73
HOMA-IR	0.04	0.49	0.06	0.29	0.05	0.37
ISSI-2	−0.04	0.50	−0.03	0.56	0.01	0.84
Insulinogenic index/HOMA-IR	−0.04	0.45	−0.02	0.72	0.04	0.55
Fasting glucose	0.05	0.40	0.06	0.27	0.01	0.83
2-h blood glucose	0.05	0.38	0.04	0.50	0.02	0.78
CRP	−0.03	0.55	0.12*	0.03*	0.21*	0.0002*

BMI, body mass index; *CRP,* C-reactive protein; *HOMA-IR,* Homeostasis Model Assessment; *ISSI-2,* Insulin Secretion-Sensitivity Index-2.
* $p<0.05$.

function and glycemia (Table 2). Baseline-adjusted change in ferritin between 1 and 3 years correlated with the concomitant change in CRP (r=0.21, p=0.0002) but was not associated with the changes in any of the metabolic factors.

On multiple linear regression analyses (Table 3), neither ferritin at 1 year nor its change from 1 to 3 years was independently associated with any of the following metabolic outcomes at 3-years postpartum: Matsuda index, HOMA-IR, ISSI-2, IGI/HOMA-IR, fasting glucose or 2-h glucose. Neither ferritin at 1 year nor the change in ferritin between 1 and 3 years predicted prediabetes and/or diabetes on forward selection logistic regression analysis (data not shown).

Discussion

In this study, we report 2 main findings. First, serum ferritin does not differ between women with recent GDM and those who did not have GDM at either 1 or 3 years postpartum. Second, neither baseline ferritin at 1 year postpartum nor its change over the 2 years thereafter is independently associated with insulin sensitivity, beta-cell function, glycemia or glucose tolerance at 3 years. It, therefore, emerges that serum ferritin is not associated with glucose homeostasis in the early years after a pregnancy complicated by GDM.

Several studies have evaluated the relationship between intrapartum measurements of ferritin and the risk of GDM. Overall, most have found a positive association between higher ferritin in pregnancy and risk of GDM (9–13); however, some have failed to detect such an association (20,21). However, few studies have examined the potential relationship between ferritin and postpartum progression to prediabetes or T2DM. Of note, among women with a history of GDM participating in the Nurses' Health Study II, those who developed T2DM reported higher intake of total iron, dietary heme iron and supplemental iron (22). Cross-sectional data from the Third National Health and Nutrition Examination Survey revealed that, among 331 women with a history of GDM, those who now had T2DM had higher serum ferritin than control subjects (women with neither previous GDM nor T2DM), whereas those who did not have T2DM (n=87) did not show elevated ferritin compared with control subjects (23). Finally, in a study of 64 women with GDM, Sharifi et al (24) found that ferritin in pregnancy did not relate to subsequent glucose levels on the OGTT at 8 weeks postpartum.

This study extends the literature by demonstrating no significant difference in serum ferritin between women with GDM and unaffected peers at both 1 and 3 years postpartum. Moreover, although both beta-cell function and insulin resistance worsen between 1 and 3 years in women with recent GDM (7), we show that neither baseline ferritin nor its change within this window relate to these changes. Accordingly, ferritin does not relate to glycemia or glucose tolerance status while this patient population experiences the early manifestation of its diabetes risk potential. It should be noted that, during the same window of time in this population, significant changes in circulating levels of adiponectin, plasminogen-activator inhibitor-1, liver enzymes and fetuin-A have been demonstrated and shown to relate to glucose homeostasis and diabetes risk (25–27). Therefore, based on our current findings, ferritin does not appear to play a significant role in determining diabetes risk in the early postpartum years after a GDM pregnancy.

A limitation of this study is that, with follow up to 3-years postpartum, these data do not exclude the possibility of iron metabolism

Table 3
Ferritin at 1 year postpartum and change in ferritin between 1 and 3 years as predictors of metabolic outcomes at 3 years postpartum

Outcome at 3 years	Predictor	Beta	t value	p value
Log Matsuda index	Ferritin at 1 year	−0.0006284	−0.63	0.53
	Change in ferritin from 1 to 3 years	0.0002813	0.25	0.81
Log HOMA-IR	Ferritin at 1 year	0.0002011	0.19	0.85
	Change in ferritin from 1 to 3 years	0.0004809	0.40	0.69
ISSI-2	Ferritin at 1 year	0.330594	0.45	0.65
	Change in ferritin from 1 to 3 years	0.566179	0.68	0.50
Log IGI/HOMA-IR	Ferritin at 1 year	−0.0015689	−0.79	0.43
	Change in ferritin from 1 to 3 years	−0.0012084	−0.53	0.60
Fasting glucose	Ferritin at 1 year	0.00053285	0.56	0.58
	Change in ferritin from 1 to 3 years	0.00130748	1.20	0.23
2-h glucose	Ferritin at 1 year	0.00120817	0.34	0.73
	Change in ferritin from 1 to 3 years	−0.0000658	−0.02	0.99

HOMA-IR, Homeostasis Model Assessment; *IGI,* insulinogenic index; *ISSI-2,* Insulin Secretion-Sensitivity Index-2.
Note: Each model was adjusted for age, ethnicity, family history of diabetes, duration of breastfeeding, body mass index at 1 year, change in body mass index from 1 to 3 years, CRP at 1 year, change in CRP from 1 to 3 years and the measure of the respective outcome variable at 1 year postpartum.

playing a role in later progression to T2DM in the years thereafter. Furthermore, the use of ferritin as a surrogate for iron metabolism may be complicated by its additional function as an acute phase reactant. That said, many previous studies have demonstrated the association of ferritin with risk of T2DM (3–6). Moreover, the current analyses were adjusted for CRP to account for the potential impact of subclinical inflammation and the acute phase response.

In summary, ferritin levels do not differ between women with recent GDM and those who did not have GDM at either 1 and 3 years postpartum. Moreover, neither baseline ferritin at 1 year postpartum nor its change over the 2 years thereafter is independently associated with insulin sensitivity, beta-cell function, glycemia or glucose tolerance at 3 years. Therefore, ferritin does not appear to be a key determinant of diabetes risk in the early postpartum years after a GDM pregnancy.

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Author Disclosures

Conflicts of interest: None.

Author Contributions

R.R. is guarantor, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. RR, AJH, PWC, and BZ designed and implemented the study. CY performed the statistical analyses. SH wrote the first draft. All authors critically revised the manuscript for important intellectual content. All authors approved the final manuscript.

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