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Correlation between plasma ferritin level and gestational diabetes mellitus and its impact on fetal macrosomia

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ABSTRACT

Aims/Introduction: To explore the relationship between plasma iron levels and gestational diabetes mellitus, as well as its impact on macrosomia.

Materials and Methods: We retrospectively compared ferritin level and other characteristics between pregnant women with gestational diabetes mellitus (GDM) and pregnant women without GDM. The correlation between the levels of plasma ferritin, glucose and hemoglobin was explored. Meanwhile, we assessed the risk factors of macrosomia. Furthermore, we explored the relationship between ferritin level and the incidence of macrosomia.

Results: A total of 793 pregnant women were enrolled in the present study, of which 92 pregnant women had GDM and 701 pregnant women were healthy. Meanwhile, 51 pregnant women gave birth to infants with macrosomia and another 742 women had normal infants. Compared with non-GDM women, pregnant women with GDM were older, with higher pre-pregnancy body mass index, plasma ferritin, fasting plasma glucose, 1-h postprandial glucose, 2-h plasma glucose and hemoglobin. In addition, our results showed a significant positive correlation between the levels of ferritin and fasting plasma glucose when ferritin levels were >70 ng/mL. Our results also showed that pre-pregnancy overweight or obesity, a high concentration of ferritin, as well as abnormal levels of fasting plasma glucose, 1-h plasma glucose and 2 h plasma glucose were risk factors for macrosomia. Furthermore, as the level of ferritin increased, so did the incidence of macrosomia.

Conclusions: The current study provides evidence that pregnant women with high levels of ferritin might be prone to GDM. In addition, a high level of ferritin might be an independent risk factor for macrosomia. Therefore, the negative effect of iron supplementation in non-anemic pregnant women might be noteworthy.

INTRODUCTION

Gestational diabetes mellitus (GDM) is one of the most common metabolic diseases during pregnancy. According to the latest report of the American Diabetes Association, it's prevalence has increased and affects up to 15–20% of all pregnancies[1], the number is 18.9% in China[2]. Previous studies showed that GDM could induce abnormal fetal development and perinatal complications, such as macrosomia[3,4]. Iron is one of the metals essential for cellular functions, which can insure normal development of the fetus and maturity of the newborn child[5]. Previous studies also showed that, in anemic pregnant women, supplementation of element iron would benefit the pregnancy outcomes, such as reducing the incidences of preterm birth[6] or low birthweight[7]. However, in addition to its positive effects, iron is associated with oxidative stress (OS) because of its catalysis for the production of hydroxyl radicals from hydrogen peroxide[8]. Rajpathak *et al.*[9] described the double-sided effect of free radicals – low levels could improve insulin sensitivity, whereas high levels are closely associated with hyperglycemia. As a consequence, a high iron level in plasma was considered a

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risk factor for GDM[10,11]. So far, very few studies have explained the correlation of plasma ferritin level with GDM, and the correlation of plasma ferritin level with fetal macrosomia has not yet been reported. In this regard, we explored the relationship between a high level of plasma ferritin and GDM, as well as the correlation of plasma ferritin level with fetal macrosomia. Furthermore, we analyzed the impact of plasma ferritin level on macrosomia in non-GDM women in order to rule out the effect of GDM. At present, elemental iron (e.g., multivitamin tablet) as a nutritional supplementation is widely used in pregnant women in China. The present study might provide a new insight into it.

METHODS

Study design

Pregnant women who gave birth at the obstetrics department and who regularly attended prenatal examinations at the obstetrics clinic (Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, Nanjing, China) from March to December 2016 were enrolled in the present study. Inclusion criteria included singleton pregnancy; aged 20–40 years; general multivitamin prophylaxis by oral supplementation (element iron 60 mg/tablet); midtrimester (24–28 weeks) screening of ferritin, 75-g oral glucose tolerance test (OGTT) and hemoglobin (Hb); and the absence of inflammation (including the absence of inflammation symptoms, but with normal levels of white blood cell counts). Initially, the data of a total of 819 pregnant women were collected according to the inclusion criteria. Exclusion criteria included women with anemia, hyperthyroidism, hypothyroidism or pregestational diabetes mellitus. A total of 26 pregnant women were excluded (anemia $n = 8$, hyperthyroidism $n = 5$, hypothyroidism $n = 10$, pregestational diabetes mellitus $n = 3$). As a result, 793 pregnant women were enrolled, of which 92 had GDM (age 30.59 ± 4.05 years) and another 701 were healthy (age 28.13 ± 4.18 years). Meanwhile, in the current study, 51 pregnant women who gave birth to infants with with fetal macrosomia were defined as a case group, and another 742 women who had normal infants were set to be a control group. Furthermore, we analyzed the impact of high plasma ferritin levels on macrosomia in 701 non-GDM pregnant women.

This study followed the ethical principles of the Helsinki Declaration.

Outcome events

In the current study, fetal macrosomia was defined as an outcome event where the birthweight of a neonate was >4,000 g. The diagnoses were taken from obstetrical medical records.

Data collection

Maternal demographic characteristics and a history of elemental iron intake were collected from the patient's maternity card (with documented pregnancy risks or documented antenatal checkups). Ferritin, plasma glucose (PG) and Hb data were from the clinic laboratory. All the data are listed in Table 1.

Stratification and definition of ferritin, body mass index and GDM

The levels of plasma ferritin in pregnant women were divided into three strata according to Milman's study[12]: <30, 30–70 and >70 ng/mL, which correspond with iron reserves being at a low level, intermediate level and high level, respectively.

Body mass index (BMI) was used to classify obesity (based on Asian cut-off points), which included four strata: underweight (<18.50 kg/m^2), normal range (18.50–23.99 kg/m^2), overweight (24.00–27.99 kg/m^2) and obesity (≥28 kg/m^2)[13].

All the participants were screened for GDM between 24 and 28 gestation weeks with the OGTT according to the

Table 1 | Maternal demographic characteristics and laboratory data

Characteristics and variables	GDM ($n = 92$)	Non-GDM ($n = 701$)	*P*-value
Age (years)	30.59 ± 4.05	28.13 ± 4.18	<0.001*†
Menarche age (years)	13.91 ± 1.11	13.92 ± 1.01	0.930†
History of cesarean section	24 (26.1%)	128 (18.3%)	0.073‡
History of miscarriage	8 (8.7%)	53 (7.6%)	0.701‡
History of induced abortion	45 (48.9%)	303 (43.2%)	0.301‡
History of premature delivery	1 (1.1%)	5 (0.7%)	1.000‡
Pre-pregnancy BMI (kg/m^2)	23.01 ± 3.91	21.73 ± 2.97	<0.001*†
Plasma ferritin (ng/mL)	25.35 (13.09, 43.24)	18.55 (10.77, 30.47)	<0.001*†
FPG (mmol/L)	5.04 ± 0.73	4.31 ± 0.34	<0.001*†
1 h-PG (mmol/L)	9.99 ± 1.57	7.06 ± 1.24	<0.001*†
2 h-PG (mmol/L)	8.16 ± 1.68	6.11 ± 0.94	<0.001*†
Hb (g/L)	121.23 ± 7.68	118.92 ± 7.21	<0.001*†

Data are presented as median (25th and 75th percentile). Data of plasma ferritin levels were normalized using log-transformation. *$P < 0.05$, gestational diabetes mellitus vs non-gestational diabetes mellitus. †The *t*-test and ‡χ^2-test. 1 h-PG, plasma glucose 1 h after the oral glucose tolerance test; 2 h-PG, plasma glucose 2 h after the oral glucose tolerance test; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus group; Hb, hemoglobin; Non-GDM, non-gestational diabetes mellitus group.

International Association of Diabetes and Pregnancy Study Groups 2010[14] and World Health Organization 2013 screening criteria[15]: plasma glucose was tested three times: at fasting, and 1 h and 2 h after glucose ingestion, respectively. A GDM diagnosis was made if one of the three values exceeded the following thresholds: fasting ≥5.1 mmol/L; 1 h ≥ 10.0 mmol/L; 2 h ≥ 8.5 mmol/L.

Statistical analysis

Categorical variables were presented as numbers with percentages, and quantitative variables with Gaussian distribution were presented as mean ± standard deviation, quantitative variables with an abnormal distribution were presented as the median with the quartile. Data of ferritin were normalized using log-transformation. Comparisons of quantitative variables between GDM and non-GDM pregnant women were assessed using Student's *t*-test for unpaired samples. Categorical variables were compared by the χ^2-test, and a value of $P < 0.05$ was considered to be statistically significant. Correlation between the level of plasma ferritin and other indexes was carried out by partial correlation analysis (adjusted by age and pre-pregnancy BMI). Meanwhile, the risk factors of macrosomia were assessed using binary logistic regression. Associations were quantified with odds ratios (OR) and their 95% confidence intervals (CI). Analyses were carried out using SPSS software (version 19.0; SPSS Inc., IBM, Armonk, NY, USA).

RESULTS

Comparison of maternal demographic characteristics and laboratory data in pregnant women with and without GDM

Among the 793 pregnant women, 92 women were diagnosed with GDM and 701 women were healthy. Our data showed that there were significant differences between the following variables: age, levels of plasma ferritin, fasting PG (FPG), 1-h PG (1 h-PG), 2-h PG (2 h-PG) and Hb in two different groups (Table 1). Compared with the controls, pregnant women with GDM were older (age 30.59 ± 4.05 years vs 28.13 ± 4.18 years), had higher levels of pre-pregnancy BMI (23.01 ± 3.91 vs 21.73 ± 2.97), plasma ferritin (25.35 [13.09, 43.24] vs 18.55 [10.77, 30.47]), FPG (5.04 ± 0.73 vs 4.31 ± 0.34), 1 h-PG (9.99 ± 1.57 vs 7.06 ± 1.24), 2 h-PG (8.16 ± 1.68 vs 6.11 ± 0.94) and Hb (121.23 ± 7.68 vs 118.92 ± 7.21). No significant differences between groups were found regarding other factors (menarche age, history of cesarean section, history of miscarriage, history of induced abortion, history of premature delivery; Table 1).

Correlation between plasma ferritin and other indexes in pregnant women in strata of ferritin levels

To further explore the correlation between plasma ferritin and other indexes, we stratified plasma ferritin levels according to previously published literature[12]. The current study suggested that there was a weak correlation between the levels of plasma ferritin and FPG ($P = 0.430$), 1 h-PG ($r = 0.089$, $P = 0.038$), 2 h-PG ($r = 0.113$, $P = 0.008$) in stratum of ferritin levels <30 ng/mL. Similarly, the present results showed that there was no correlation between the levels of plasma ferritin and FPG ($P = 0.164$), 1 h-PG ($P = 0.059$), 2 h-PG ($P = 0.065$) in stratum of ferritin levels between 30 and 70 ng/mL. Whereas, in stratum of ferritin levels >70 ng/mL, our results showed the positive correlation between the levels of plasma ferritin and FPG ($r = 0.461$, $P = 0.002$), except for 1 h-PG ($P = 0.269$) and 2 h-PG ($P = 0.245$). In addition, our data also showed the positive correlation of plasma ferritin levels with Hb, which was only present in a low concentration of plasma ferritin (<30 ng/mL; $r = 0.215$, $P < 0.001$; Table 2).

Multivariate analysis for maternal characteristics and laboratory data on fetal macrosomia

We carried out multivariate analysis for maternal characteristics and laboratory data by using binary logistic analysis. Our results showed that pre-pregnancy overweight (bodyweight 24–27.99 kg/m^2; OR 15.734, 95% CI 1.984–124.796) and obesity (bodyweight >28 kg/m^2; OR 26.257, 95% CI 2.695–255.796), high concentration of plasma ferritin (>70 ng/mL; OR 3.191, 95% CI 1.247–8.167), as well as abnormal levels of FPG, 1 h-PG and 2 h-PG (OR 5.322, 95% CI 1.663–17.034) were, respectively, independent risk factors for macrosomia, and that the effect of plasma ferritin could not be adjusted by plasma glucose and pre-pregnancy BMI (Table 3).

Stratified analysis for fetal macrosomia by plasma ferritin levels in non-GDM pregnant women

In order to only focus on the effect of plasma ferritin on macrosomia outcome, without regard to the roles glucose might play, we analyzed their correlation in non-GDM pregnant women. Our results showed that there was still a correlation between plasma ferritin level and fetal macrosomia in non-GDM pregnant women. Meanwhile, in the stratum of plasma ferritin level >70 ng/mL, the outcome events occurred more frequently (15.15%) than those in 30–70 ng/mL level (6.18%),

Table 2 | Stratified analysis for plasma ferritin levels and other laboratory data

Variables	Ferritin <30 ng/mL		Ferritin 30–70 ng/mL		Ferritin >70 ng/mL	
	r	*P*-value†	*r*	*P*-value†	*r*	*P*-value†
FPG (mmol/L)	0.034	0.430	0.097	0.164	0.461	0.002*
1 h-PG (mmol/L)	0.089	0.038*	0.131	0.059	0.170	0.269
2 h-PG (mmol/L)	0.113	0.008*	0.128	0.065	0.179	0.245
Hb (g/L)	0.215	<0.001*	–0.137	0.050	0.206	0.179

**P*-value for correlation coefficient detected by partial correlation analysis. †Partial correlation analysis (Adjusted by age and pre-pregnancy body mass index). Levels of plasma ferritin: <30 ng/mL, low level; 30–70 ng/mL, intermediate level; >70 ng/mL, high level. 1 h-PG, plasma glucose 1 h after the oral glucose tolerance test; 2 h-PG, plasma glucose 2 h after the oral glucose tolerance test; FPG, fasting plasma glucose; Hb, hemoglobin.

Table 3 | Multivariate analysis for maternal characteristics and laboratory data according to fetal macrosomia outcomes

Covariates	No. participants	No. events	Odds ratio (95% CI)	*P*-value†
Overall	793	51		
Age (years)				
<25	187	9		
25–29.99	391	21	0.876 (0.378–2.026)	0.756
30–34.99	161	17	1.431 (0.561–3.652)	0.453
≥35	54	4	0.952 (0.246–3.688)	0.943
Menarche age (years)				
<13	48	1		
13–14	571	43	2.866 (0.376–21.832)	0.310
>14	174	7	1.287 (0.148–11.185)	0.819
History of cesarean section				
No	641	36		
Yes	152	15	1.046 (0.490–2.232)	0.908
History of miscarriage				
No	732	44		
Yes	61	7	1.552 (0.624–3.860)	0.345
History of induced abortion				
No	445	26		
Yes	348	25	0.998 (0.529–1.884)	0.996
History of premature delivery				
No	787	51		
Yes	6	0	0.000	0.999
Pre-pregnancy BMI (kg/m^2) (kg/m^2)				
<18.50	102	1		
18.50–23.99	507	24	5.986 (0.774–46.270)	0.086
24.00–27.99	158	21	15.734 (1.984–124.796)	0.009*
≥28	26	5	26.257 (2.695–255.796)	0.005*
Serum ferritin (ng/mL)				
<30	542	30		
30–70	207	13	0.946 (0.465–1.928)	0.879
>70	44	8	3.191 (1.247–8.167)	0.016*
FPG × PG(1 h) × PG(2 h) (mmol/L)				
normal	775	45		
Abnormal	18	6	5.322 (1.663–17.034)	0.005*

*$P < 0.05$ vs body mass index <18.5, vs serum ferritin <30 ng/mL and vs FPG × PG (1 h) × PG (2 h) normal, factors significantly associated with macrosomia. †Binary logistic regression. 1 h-PG, plasma glucose 1 h after the oral glucose tolerance test; 2 h-PG, plasma glucose 2 h after the oral glucose tolerance test; FPG, fasting plasma glucose; FPG × PG (1 h) × PG (2 h), the interaction of plasma glucose at different periods.

as well as than those in the <30 ng/mL level (4.90%). Furthermore, as the level of plasma ferritin increased, the incidence of macrosomia increased (*P* for trend = 0.042; Table 4).

Table 4 | Stratified analysis for fetal macrosomia in pregnant women without gestational diabetes

Ferritin (ng/mL)	*n*	Cases (*n* = 40)	Controls (*n* = 661)
<30	490	24 (4.90%)	466 (95.10%)
30–70	178	11 (6.18%)	167 (93.82%)
>70	33	5 (15.15%)	28 (84.85%)

P for trend = 0.042. Cases, with fetal macrosomia outcome; Controls, without fetal macrosomia outcome.

DISCUSSION

Gestational diabetes mellitus increases the risks of maternal, fetal and neonatal complications, which make it a serious public health challenge. Iron is associated with OS, which is considered a risk factor for GDM[16,17]. Iron supplements are not recommended when the plasma ferritin level is >70 ng/mL[12]. In developed countries, iron prophylaxis is recommended for pregnant women according to their plasma level of ferritin. Nevertheless, most pregnant women receive general iron prophylaxis by oral supplementation regardless of their plasma iron levels in China. However, there is no related study pertaining to the correlation of plasma ferritin level with macrosomia in the Chinese population so far. In addition, to rule out the positive impact of elemental iron intake on anemic pregnant women, these women were excluded from our current study, which focused on the exploration of the negative effect of high plasma ferritin levels

on pregnant women. We carried out a retrospective study to explore the correlation between plasma ferritin level and GDM, as well as its impact on macrosomia in non-anemic pregnant women in the Chinese population. In the current study, consistent with previous data[18], we found that there were higher levels of plasma ferritin, pre-pregnancy BMI, Hb and PG in GDM women who were older, compared with non-GDM women (Table 1). In order to further explore the correlation between plasma ferritin level and PG and Hb, we carried out stratified analysis according to the levels of plasma ferritin at <30, 30–70 and >70 ng/mL, respectively, which was considered low level, intermediate and high level, respectively[12]. At a low level of plasma ferritin (<30 ng/mL), there was a weak positive correlation between ferritin and PG, but there was a moderate correlation between ferritin and Hb, indicating a beneficial and risk-free effect by prophylaxis of iron supplementation. At a high level of plasma ferritin (>70 ng/mL), the correlation between ferritin and FPG was remarkably strengthened, suggesting the tight association of a high level of plasma ferritin with GDM (Table 2), which is consistent with a previous study[19].

The association between high plasma ferritin level and GDM has been known for the past few years; furthermore, we also analyzed the correlation between PG and ferritin level by stratification in the present study. However, whether a high level of plasma ferritin was associated with fetal macrosomia has been unclear so far. Several previous studies suggested that FPG screening did not completely meet the requirement, and postprandial glucose determination was essential[20]. In the current study, we also found that PG (including FPG, 1 h-PG, 2 h-PG) was a strong risk factor for fetal macrosomia, and that effect was not adjusted by the other factors. However, Olmos *et al.*[21] showed that glycemic control in GDM patients was not enough to reduce macrosomia, and that iron supplementation was positively correlated with birthweight[22]. We carried out multivariate regression analysis, showing that a high level of plasma ferritin (>70 ng/mL) was an independent risk factor for macrosomia, which could not be adjusted by PG and pre-pregnancy BMI (Table 3). To exclude the effect of GDM, we further explored the effect of high plasma levels of ferritin on macrosomia in non-GDM pregnant women. The results showed that there was a significant difference in the macrosomia outcome by stratified ferritin levels. The incidences of macrosomia were higher at the level of plasma ferritin >70 ng/mL than those at low levels and intermediate levels of plasma ferritin (<30 and 30–70 ng/mL), respectively. Importantly, as the level of ferritin increased, the incidences of macrosomia also increased (Table 4).

The present study suggested that a high level of plasma ferritin was associated with macrosomia, even though the pregnant women did not have GDM. Several previous studies reported that moderate iron intake in non-anemic pregnant women could induce glycemic disorder, hyperinsulinemia and oxidative damage in their offspring[23], and that fetal hyperinsulinemia was positively correlated with macrosomia[21]. Interestingly, both pregnant women and their newborns showed euglycemia after treatment with diet; however, metabolic alternation of OS in the fetoplacental vasculature was seen, including endothelial dysfunction[24], which was likely associated with hyperinsulinemia of the fetus and thereby leading to macrosomia. Although their PG was normal, non-GDM pregnant women with a high concentration of plasma ferritin might induce fetal hyperinsulinemia and oxidative damage in their offspring, leading to metabolic alternation by OS; thereby, it was likely associated with macrosomia. A previously published study reported that the fetal hyperinsulinemia could suppress the peak of PG in pregnant women, consequently, OGTT results in these pregnant women might be mistaken for normal[25]. An interesting finding was shown in some cases that OGTT could not completely detect all cases of GDM. Therefore, examining other indexes (e.g., fetal insulin) for GDM and adverse pregnant outcome would be important. However, it is impossible to carry out insulin measurement of amniotic fluid widely in pregnant women. Consequently, ferritin might be one of the key indicators. Thus, based on the present strategy of Chinese GDM screening by OGTT, we should acknowledge that the study participants perhaps still could be diagnosed as GDM after the period between weeks 24 and 28 of gestation, which could interfere with the present results and was an imperfection of our study.

In previously published studies regarding women in preterm labor, the results regarding ferritin levels were controversial[26–28]. Hou *et al.*[29] suggested that there was a high level of maternal serum ferritin in asymmetrical intrauterine growth restriction (IUGR), whereas it was low in symmetrical IUGR. However, they speculated that ferritin as an acute phase protein was increased in inflammation, and did not directly induce IUGR. Furthermore, up to 47% of study participants in that study had anemia, and anemia was closely associated with IUGR. Therefore, the authors showed that when anemia was severe, there was an association between the level of ferritin and low birthweight; however, when anemia was moderate, the association was not clear[30]. Consequently, the association between the level of ferritin and IUGR is circumstantial, ferritin might be an insufficient screening indicator for preterm labor and IUGR[31]. It seems the inconsistency between the present results and those of some other published studies might be due to the different inclusion criterion for study participants, to the different conditions of fetal intrauterine growth, and to the presence or absence of inflammation among the pregnant women.

Taken together, a high level of plasma ferritin might be closely associated with GDM; furthermore, it might also be associated with macrosomia regardless of whether pregnant women had GDM or not. The current study might suggest that iron supplementation should be individually based on the plasma level of ferritin, and that caution must be exercised in regard to multivitamin tablets being taken by pregnant women with high plasma ferritin levels.

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DISCLOSURE

The authors declare no conflict of interest.

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