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ORIGINAL RESEARCH

Serum Ferritin Levels in Pregnancy and Their Association with Gestational Diabetes Mellitus: A Prospective Longitudinal Study

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Objective: Elevated serum ferritin (SF) levels are associated with oxidative stress (OS) and systemic inflammation in various disorders. However, the changes in SF levels during pregnancy and their relationship with gestational diabetes mellitus (GDM) and blood glucose levels are not well understood.

Methods: This prospective longitudinal study included 390 participants (130 GDM cases and 260 controls) during early pregnancy. We measured SF levels in the1st, 2nd, and 3rd trimesters, as well as plasma malondialdehyde (MDA) and C-reactive protein (CRP) in the 1st trimester, blood glucose levels in the oral glucose tolerance test (OGTT), and glycosylated hemoglobin (HbA1c) in the 2nd trimester. We used Spearman's rank correlation to estimate the association between SF, OS, inflammation and glucose levels. Logistic regression analysis was performed to estimate the OR of GDM associated with SF. Multiple stepwise regression models were used to assess the relationship between glucose levels and the risk factors.

Results: SF levels decreased with increasing gestation in the study population. Compared to controls, GDM patients had significantly higher levels of SF (1st and 2nd trimesters), MDA, CRP, and HbA1c. SF was positively correlated with MDA and fasting plasma glucose (FPG). Elevated SF levels during early pregnancy were significantly associated with increased GDM risks (OR = 2.024, 95% CI: 1.076 – 3.807). The explanatory variables that contributed to increased glucose levels were SF, MDA, body mass index (BMI), maternal age, and family history of diabetes.

Conclusion: SF is significantly associated with GDM and may be a potential biomarker for GDM in early pregnancy.

Keywords: gestational diabetes mellitus, ferritin, oxidative stress, inflammation

Introduction

Gestational diabetes mellitus (GDM) is a common pregnancy complication characterized by abnormal glucose tolerance, with onset or first recognition during pregnancy.[1] GDM affects approximately 17% of pregnancies worldwide, and its prevalence has increased significantly in recent decades.[2] The condition is associated with various adverse outcomes, including preterm delivery, macrosomia, abortion, respiratory distress, stillbirth, neonatal death, and increased caesarean section (C-section) delivery, making it a leading cause of perinatal morbidity and mortality in mothers and children.[3] Furthermore, mothers and children affected by GDM are at a higher risk of developing metabolic syndrome, type 2 diabetes mellitus (T2DM), and cardiovascular diseases later in life.[4,5] Although the underlying mechanisms of GDM

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development are not yet fully understood, research suggests that oxidative stress (OS) and chronic inflammation play a crucial role in the pathogenesis of GDM.[6,7]

Serum ferritin (SF) is a biomarker of body iron storage. Elevated SF levels may indicate the degree of OS and systemic inflammation. When the amount of iron in the plasma exceeds the iron-binding capacity of transferrin, non-transferrin-bound iron acts as a strong oxidant, generating hydroxyl radicals via the Fenton reaction.[8] These reactive oxygen species (ROS) can cause oxidative damage to biomacromolecules, including nucleic acids, proteins, and lipids.[9] OS can activate the inflammatory response, characterized by the persistent secretion of cytokines and chemokines, which disrupts insulin signaling and interferes with energy metabolism.[10] Inflammation, in turn, enhances OS, and these two processes are closely linked and interdependent.[11] Studies have shown that plasma/serum malondialdehyde (MDA), a marker of polyunsaturated fatty acids peroxidation, and inflammatory marker like C-reactive protein (CRP) are significantly elevated in GDM.[7] Pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor α (TNF-α), can stimulate ferritin expression via the nuclear factor (NF)-κB pathway.[12] Additionally, as an iron storage protein, ferritin can be induced in response to iron overload through the interaction of iron-responsive elements (IRE) on ferritin-encoding RNAs with iron regulatory proteins (IRP).

We aimed to investigate the changes in SF levels during pregnancy and explore the potential connections between SF levels, OS, and inflammation during pregnancy, as well as their possible relationship with GDM and blood glucose levels. Elucidating these connections could provide valuable insights into the underlying mechanisms of GDM. To achieve this goal, we conducted a prospective longitudinal study involving 130 GDM cases and 260 controls in early gestation. We employed Spearman's rank correlation, logistic regression, and multiple stepwise regression analyses to examine the association of SF levels with GDM and blood glucose levels related to OS and inflammation.

Materials and Methods

Study Design and Participants

This prospective longitudinal study was conducted within a birth cohort established at the Second Affiliated Hospital of Guilin Medical University between June 2021 and December 2022. Participants were recruited based on the following inclusion criteria: (1) age 20–40 years; (2) singleton natural pregnancy; (3) regular prenatal care and delivery at the hospital; and (4) completed laboratory assays and medical records. Exclusion criteria included pregnant women with chronic diseases, such as type 1 or type 2 diabetes, hypertension, malignancy, hypothyroidism, acute or chronic inflammatory or infectious diseases, iron deficiency anemia, liver and kidney diseases, and mental disorders. Additionally, participants with unverifiable information were excluded. Among the 850 pregnant women screened, 130 GDM cases of GDM were ultimately recruited and matched with 260 controls (1:2 ratio) by gestational age (± 1 week) in the same period (Figure 1). To minimize the sampling error and enhance the statistical power, we doubled (GDM cases) or quadrupled (controls) the sample size (64 for each group), which was calculated using G*Power software, assuming a medium effect size, two-sided testing, a significance level of $\alpha = 0.05$, and a power of $1 - \beta = 0.8$.[13] GDM was diagnosed by medical professionals at the hospital according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria.[14] Specifically, an oral glucose tolerance test (OGTT) was conducted between 24 and 28 weeks of gestation, and GDM was diagnosed if one or more of the following glucose levels were met: fasting plasma glucose (FPG) ≥ 5.1 mmol/L, 1-h plasma glucose (OGTT-1h) ≥ 10.0 mmol/L, or 2-h plasma glucose (OGTT-2h) ≥ 8.5 mmol/L. This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. All participants provided informed consent, and the study was approved by the Ethics Committees of Guilin Medical University.

Information Collection

Trained research staff conducted face-to-face interviews with participants to collect demographic and lifestyle information, including maternal age, weight, height, blood pressure, ethnicity, education, occupation, smoking status, alcohol consumption, economic status, family history of diabetes, history of GDM, and dietary supplement intake. Body mass index (BMI) was calculated by dividing weight (in kg) by height (in m^2). To ensure accurate blood pressure measurements, participants

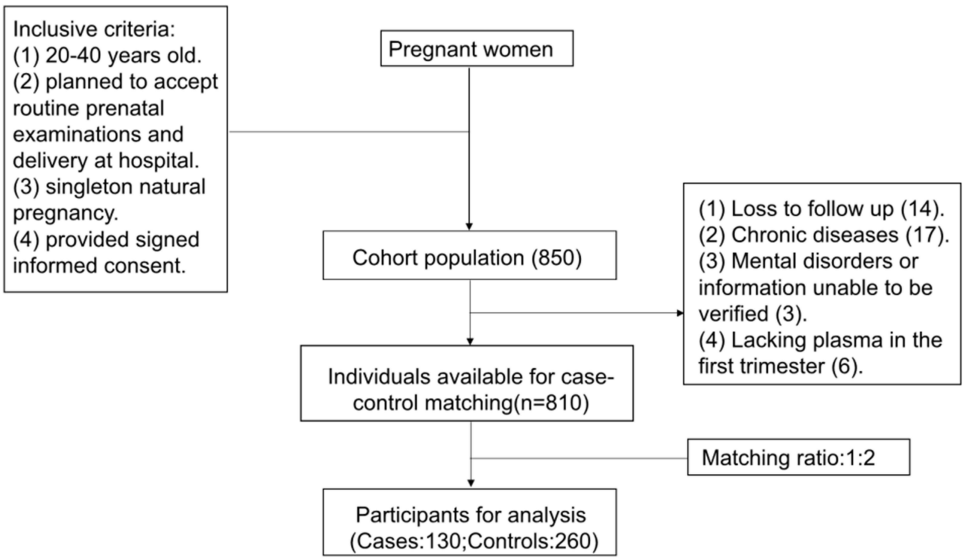

Figure 1 Subject inclusion and exclusion flow chart.

were seated and rested for at least 10 min before measurement. Blood pressure was measured twice on the left upper arm using a random zero sphygmomanometer, and the average of the two readings was used for analysis. Additional information on pregnancy complications and medical treatments was obtained from the hospital's electronic health records.

Biochemical Index Determination

All biochemical indexes were measured by the clinical laboratory at the hospital. Fasting venous blood samples were collected from pregnant women at 10–14, 24–28, and 36–39 weeks of gestation. SF was measured using a coated tube immunoradiometric assay with Elecsys Ferritin kit. CRP was measured using a high sensitivity assay with the C-reactive protein test kit, which employs a latex particle-enhanced immunoturbidimetric assay. Plasma glucose levels were measured using Glucose Hexokinase_3 Reagents (GLUH_3). Glycosylated hemoglobin (HbA1c) (normal range 4.8–6.2%) was measured using the Glycated Hemoglobin Determination Kit, which utilizes a latex-enhanced turbidimetric Immunoassay method. All of these kits were obtained from Roche. Biochemical assays were conducted using a C8000 automatic analyzer (Roche Diagnostics). MDA was determined using the Malondialdehyde assay kit (TBA method) purchased from Nanjing Jiancheng Biological Engineering Co., Ltd. All analyses were performed according to the manufacturer's instructions.

Statistical Analysis

Statistical analyses were performed using SPSS27.0. Quantitative data were presented as mean ± standard deviation (SD) or median (25^{th} - 75^{th} percentile), while qualitative data were presented as frequency. Differences in the demographic characteristics and biochemical assays between GDM and control groups were assessed using Student's *t*-test, Mann–Whitney *U*-test, analysis of variance (ANOVA), and Chi-squared test. Correlations between SF, MDA, CRP, BMI, FBG, OGTT-1h, OGTT-2h, and HbA1c were analyzed using Spearman's rank correlation. Conditional logistic regression analyses were performed to examine the association between SF and the risk of GDM. Additionally, stepwise regression analyses were used to estimate the impact of independent variables on glucose levels and GDM. A two-tailed p-value < 0.05 was considered statistically significant for all analyses.

Results

Demographic Characteristics of Study Populations

The study recruited 130 GDM cases and 260 normoglycemic pregnant women during early pregnancy. The demographic characteristics of the study populations were presented in Table 1. Compared to the control group, the GDM group had

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significantly higher maternal age, BMI, and a higher rate of family history of diabetes ($P < 0.05$). The two groups were comparable in terms of other demographic characteristics (Table 1).

Biochemical Indexes in GDM

Compared to the controls, the GDM group had significantly higher levels of FPG, OGTT-1h, OGTT-2h, HbA1c, MDA, and CRP. SF levels decreased significantly from the 2nd to the 3rd trimester in both groups compared to the 1st trimester. However, SF levels were significantly higher in the GDM group compared to the control group during the 1st and 2nd trimesters (Table 2).

Correlations Between Biochemical Indexes and Demographic Characteristics

Spearman correlation analysis revealed that SF at the 1st trimester was positively correlated with MDA (r = 0.101, P = 0.046) and FPG (r = 0.107, P = 0.035). MDA was significantly correlated with CRP (r = 0.126, P = 0.013), FPG (r = 0.108, P = 0.032), and OGTT results at 1 and 2 hours (r = 0.194, $P < 0.001$ and r = 0.205, $P < 0.001$, respectively). CRP was positively associated with FPG (r = 0.162, P = 0.001), OGTT-1h (r = 0.216, $P < 0.001$), OGTT-2h (r = 0.166, P = 0.001), and HbA1c (r = 0.211, $P < 0.001$). Additionally, maternal age and BMI were correlated with MDA, CRP, and blood glucose levels (Figure 2).

Association of Serum Ferritin with GDM

Conditional logistic regression analysis revealed a significant association between SF levels at the 1st trimester and GDM. The ORs increased significantly with higher SF levels, with a 1.83-fold increase (95% CI: 1.009–3.319) in the non-adjusted model when comparing the highest quartile (Quartile 4) to the lowest quartile (Quartile 1). After adjusting for maternal age, BMI, and family history of diabetes, the association became even more pronounced (OR = 2.024, 95% CI: 1.076–3.807) (Table 3).

Influence of SF, MDA, CRP, and Demographic Characteristics on Blood Glucose Levels

Stepwise multiple regression analysis was performed to examine the relationships between maternal age, BMI, 1st trimester SF, MDA, CRP, and family history of diabetes (independent variables) and FPG, OGTT results at 1 and 2 hours (dependent variables). The results showed that BMI, 1st trimester SF, and maternal age were significant explanatory variables for increased FPG in the study population (adjusted $R^2 = 15.7$, $P < 0.001$). Similarly, maternal age, BMI, and MDA were significant explanatory variables for increased OGTT-1h (adjusted $R^2 = 11.6$, $P < 0.001$). For OGTT-2h, maternal age, BMI, MDA, and family history of diabetes were the significant explanatory variables (adjusted $R^2 = 12.5$, $P < 0.001$) (Table 4).

Discussion

In this study, we found that SF levels were significantly elevated in the 1st and 2nd trimesters among GDM patients compared with controls, and decreased with the progress of pregnancy until the 3rd trimester in both groups. Additionally, plasma MDA, CRP, and HbA1c levels increased in GDM. The 1st trimester SF was positively correlated with MDA and FPG, and significantly associated with GDM. Furthermore, the 1st trimester SF, MDA, BMI, maternal age, and family history of diabetes were explanatory variables for increased glucose levels. Our findings suggest that SF may be a potential biomarker for the early phase of GDM.

Iron is an essential element that participates in various metabolic processes in humans, including oxygen transport, DNA synthesis, immunity, cell division and differentiation, and energy metabolism.[15] SF levels reflect iron storage in the body.[8] In this study, we found that SF levels were relatively high in the 1st trimester and decreased as the pregnancy progressed, suggesting an increasing iron requirement for the mother's health and fetal development during pregnancy.[16] While iron deficiency can cause adverse health effects, such as iron deficiency anemia, the damage caused by iron overload may be more significant.[17] Excess iron, a transition metal with redox activity, plays a crucial role in the production of ROS, including hydroxide (OH^-) and hydroxyl radical ($HO^{\cdot}$), through Fenton reactions.[18] When ROS production exceeds physiological levels, various cell signaling pathways, including insulin receptor substrate-1 (IRS-1),

Table 1 Demographic Characteristics of the Study Populations

Characteristic	Control (n=260)	GDM (n=130)	*P*-value
Maternal age (years)	29.60 ± 4.12	31.81 ± 4.05	<0.001
Gravidity	2.63 ± 1.44	2.92 ± 1.58	0.068
Parity	1.76 ± 0.71	1.87 ± 0.74	0.157
BMI (kg/m^2)	21.11 ± 2.71	22.50 ± 3.04	<0.001
SBP (mmHg)	107.30 ± 10.82	106.90 ± 7.58	0.709
DBP (mmHg)	66.38 ± 7.08	65.33 ± 4.65	0.081
Ethnicity			0.626
Han	220 (84.6)	110 (84.6)	
Zhuang	25 (9.6)	15 (11.5)	
Others	15 (5.8)	5 (3.9)	
Education			0.055
Less than high-school graduate	143 (55)	55 (42.3)	
Junior college	43 (16.5)	30 (23.1)	
More than high-school	74 (28.5)	45 (34.6)	
Occupation			0.054
Official	112 (43.1)	75 (57.5)	
Non-official	12 (4.7)	6 (4.8)	
Freelancer	136 (52.3)	49 (37.7)	
Household income (CNY)			0.093
0-	8 (3.1)	8 (6.2)	
30,000-	124 (47.7)	49 (37.6)	
100,000-	128 (49.2)	73 (56.2)	
Family history of diabetes			0.025
Yes	6 (2.3)	9 (6.9)	
No	254 (97.7)	121 (92.1)	
Smoking during pregnancy			-
Yes	0 (0)	0 (0)	
No	260 (100)	130 (100)	
Drinking alcohol during pregnancy			0.341
Yes	16 (6.2)	5 (3.8)	
No	244 (93.8)	125 (96.2)	
History of prior GDM			0.383
Yes	3 (1.1)	3 (2.3)	
No	257 (98.9)	127 (97.7)	
Folic acid supplementation			0.090
Daily	238 (91.5)	110 (84.6)	
Occasionally	13 (5)	9 (6.9)	
Never	9 (3.5)	11 (8.5)	
Mineral supplementation			0.563
Daily	14 (5.4)	5 (3.8)	
Occasionally	6 (2.3)	5 (3.8)	
Never	240 (92.3)	120 (92.3)	
Multivitamin supplementation			0.571
Daily	16 (6.2)	6 (4.6)	
Occasionally	14 (5.4)	10 (7.7)	
Never	230 (88.5)	114 (87.7)	

Note: Data in the table were means ± SD or n (%) and tested using independent samples *t*-test or Chi-square test.

Abbreviations: BMI, body mass index; CNY, Chinese yuan; DBP, diastolic blood pressure; GDM, gestational diabetes mellitus; SBP, systolic blood pressure.

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Table 2 Comparison of Biochemical Indexes Between the GDM and Control Groups

Variables	Control (260)	GDM (130)	*P*-value
2nd FPG (mmol/l)	4.60 ± 0.27	5.00 ± 0.47*	<0.001
2nd OGTT-1h (mmol/l)	7.35 ± 1.40	9.16 ± 1.76*	<0.001
2nd OGTT-2h (mmol/l)	6.39 ± 1.03	7.90 ± 1.55*	<0.001
2nd HbA1c (%)	4.77 ± 0.50	4.99 ± 0.36*	<0.001
1st MDA (nmol/mL)	3.78 (2.5–5.43)	5.49 (4.4–6.95)*	<0.001
1st CRP (mg/L)	2.76 (1.26–5.26)	3.80 (1.53–6.50)*	0.019
1st SF (ng/mL)	89.49 (53.14–133.73)	102.15 (57.03–161.25)*	0.040
2nd SF (ng/mL)	31.33 (18.87–49.16)##	35.72 (23.43–56.09)*##	0.039
3rd SF (ng/mL)	31.10 (20.20–44.71)##	32.22 (18.48–53.88)##	0.657

Notes: Data in the table were means ± SD or medians (25th - 75th percentile), and tested by using independent samples *t*-test or Mann Whitney *U*-test. *$P < 0.05$ compared with controls; ##$P < 0.01$ compared with the 1st trimester in the same group. 1st, during 10–14 weeks of pregnancy; 2nd, during 24–28 weeks of pregnancy; 3rd, during 36–39 weeks of pregnancy.

Abbreviations: FPG, fasting plasma glucose; OGTT-1h, plasma glucose level at 1 h after the oral glucose tolerance test (OGTT); OGTT-2h, plasma glucose level at 2 h after the OGTT; HbA1c, glycosylated hemoglobin; MDA, malondialdehyde; CRP, C-reactive protein; SF, serum ferritin.

insulin receptor (IR), insulin or insulin-like growth factor (IGF-1), ERK kinases, and PI3K/Akt, are impaired, leading to decreased insulin secretion and potentially insulin resistance.[19] Furthermore, pancreatic islets express low levels of antioxidants, such as superoxide dismutase, catalase, and glutathione peroxidase, making β-cells particularly vulnerable to oxidative damage.[20] Our study found that SF levels were significantly higher in GDM women during the 1st and 2nd trimesters compared to controls, suggesting a connection between high iron storage and GDM. Previous studies have shown that OS derived from iron can decrease muscle glucose uptake and consumption, while increasing gluconeogenesis in the liver, resulting in a predisposition to GDM.[21,22] In our study, plasma MDA and CRP levels were increased in the GDM group, and SF was correlated with MDA, indicating a link between iron and OS in GDM. These findings support the proposal that iron supplements during pregnancy should be taken only in specific situations, such as iron deficient anemia.[23] We found a positive and significant association between SF and GDM risk, even after adjusting for plasma CRP levels and several risk factors for GDM, including maternal age and BMI. This finding is consistent with a prospective cohort study in China, which reported a two-fold increased risk of developing GDM among women in the highest quintile of SF.[23] Similarly, Cheng et al found that high ferritin levels (greater than 87.2 μg/L) increased the risk of GDM by 2.31-fold (95% CI: 1.30–4.10, $P = 0.018$) compared to the lowest levels, even after adjusting for potential confounders factors.[24] High levels of SF in mid-pregnancy have also been positively correlated with the risk of GDM.[25] However, Zein et al reported no significant association between high SF levels and the incidence of GDM in early pregnancy, possibly due to the low overall SF concentrations in the study and the relatively low cut-off value for the highest SF concentration quartile (38.5 μg/L) compared to our study (139.6 μg/L).[26] A randomized controlled trial found no association between iron supplementation and GDM, which may be attributed to the varying body iron stores, and different dosages and durations of iron supplementation in different pregnant populations.[27]

To further explore the effects of SF, oxidative stress, and inflammation on blood glucose levels, we performed stepwise regression analysis. Our results showed that 1st trimester SF, MDA, BMI, and maternal age were significant explanatory factors for high blood glucose levels, confirming that iron overload plays a key role in the occurrence and development of GDM. BMI and age may increase the risk of GDM due to higher oxidative stress and inflammation in individuals with higher BMI, as well as decreased antioxidant capacity with age and accumulated oxidative damage.[28,29] These findings are consistent with the established risk factors for GDM, including BMI and maternal age.[30] Pregnant women with higher BMI tend to have more severe OS and inflammation, and antioxidant capacity decreases with age, leading to accumulated oxidative damage.[28,29] Iron overload may exacerbate OS and contribute to the disturbance of metabolic homeostasis during GDM development.

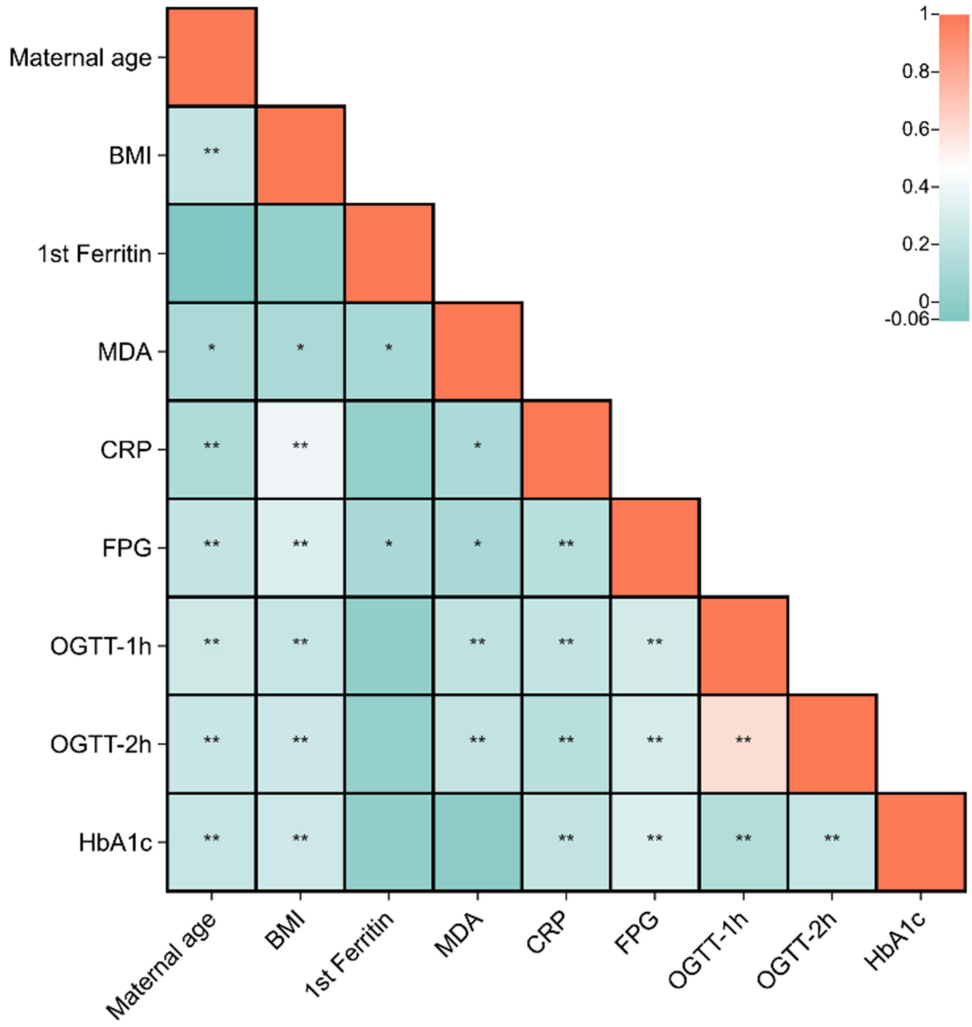

Figure 2 Correlation between maternal age, BMI, and biochemical indexes. The color key represents the regression coefficients of the independent variables. Only statistically significant correlations are displayed in the figure. *$P < 0.05$, **$P < 0.01$.

Our study has several strengths. Firstly, we detected SF levels in early pregnancy before the diagnosis of GDM, which minimizes the potential impact of GDM on SF levels. Secondly, we evaluated the longitudinal changes in SF levels in pregnant women and estimated the relationship between SF and GDM. Finally, we determined OS and inflammatory

Table 3 Association of Serum Ferritin in Early Gestation with GDM

		Serum ferritin at 10–14 weeks of gestation (μg/L)			
		Quartile 1 ≤ 54.1	**Quartile 2 54.2–91.7**	**Quartile 3 91.8–139.6**	**Quartile 4 > 139.6**
GDM	N (%)	98 (28.57)	97 (30.93)	98 (31.63)	97 (42.27)
Model 1	*P*	Ref	0.719	0.64	0.047
	OR		1.119	1.157	1.83
	95% CI		0.606–2.069	0.628–2.131	1.009–3.319
Model 2	*P*	Ref	0.586	0.429	0.029
	OR		1.197	1.302	2.024
	95% CI		0.626–2.287	0.677–2.504	1.076–3.807

Notes: The association between SF and GDM was identified at the highest quartile (Quartile 4) of SF, with Quartile 1 as the reference. Model 1: Unadjusted analysis. Model 2: Adjusted analysis for maternal age, BMI, CRP, and family history of diabetes.
Abbreviations: OR, odds ratio; CI, confidence interval.

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Table 4 Stepwise Regression Analyses for Glucose Levels in OGTT

Stepwise Regression Models	β	*P*	Adjusted R^2
FPG		< 0.001	15.7
BMI	0.042	<0.001	
1st SF	0.001	<0.001	
Maternal age	0.013	0.005	
OGTT-1h		< 0.001	11.6
Maternal age	0.091	<0.001	
BMI	0.113	<0.001	
MDA	0.083	0.010	
OGTT-2h		< 0.001	12.5
Maternal age	0.070	<0.001	
BMI	0.093	<0.001	
MDA	0.077	0.003	
Family history of diabetes	0.748	0.033	

Notes: Variables in the analysis included: maternal age, BMI, 1st SF, MDA, CRP, and family history of diabetes.

biomarkers, allowing us to examine the relationship between iron storage, OS, and inflammation before the onset of GDM. However, our study also has a limitation. We lacked data on dietary iron intake and iron supplementation, which prevented us from exploring the relationship between iron supplementation and the development of GDM.

Conclusion

In conclusion, our study found that SF levels significantly increase during early pregnancy in GDM and are positively associated with GDM, suggesting that SF may be a potential early phase biomarker of GDM. Further research is needed to elucidate the underlying mechanisms and to explore the potential utility of SF as a biomarker for GDM.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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