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RESEARCH

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Associations between serum ferritin levels and gestational diabetes mellitus among a non-anemic population

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Abstract

Background Studies have shown a strong correlation between excess iron and the development of gestational diabetes mellitus (GDM), though iron is an essential trace element during pregnancy. This study aims to investigate the precise relationship between iron storage levels during late pregnancy and the development of GDM, trying to find out ways to meet pregnant iron storage requirements and reduce GDM risk simultaneously.

Methods A non-anemic population consisting of 9,512 healthy singleton pregnant women were included in this study. Serum ferritin (SF) levels during the second and third trimesters and other clinical information were retrospectively collected. Restricted cubic splines (RCS) were performed to examined the non-linear associations between SF level and the GDM incidence as well as blood glucose related indicators during the second trimester. Moreover, the association between the variation of HbA1c levels and the fluctuation of SF levels throughout the third trimester was also explored with the method of RCS.

Results Overall, women with GDM had slightly higher median SF level than women without GDM 20.5 (13.3, 32.3) vs. 19.8 (12.9, 30.5), $P=0.017$) in the second trimester. A U-shaped relationship between GDM risk and SF levels in the second trimester was established after accounting for other cofounding factors ($P<0.001$ for nonlinearity). Both GDM and non-GMD women revealed a significant negative relationship between hemoglobin A1c (HbA1c) and SF levels ($P<0.001$ for nonlinearity for both). The 1-hour post-glucose load plasma glucose showed a positive correlation tendency with SF levels ($P=0.748$ for nonlinearity) in GDM women, while the relationship between these two variables was not obvious in non-GDM women ($P=0.045$ for nonlinearity). Generally, the levels of HbA1c rose in the trimester, however, maintaining a high SF level throughout the third trimester would substantially increase the HbA1c level among GDM women with high SF levels (>30ng/ml) in the second trimester ($P<0.001$ for nonlinearity).

Conclusions GDM might result from high or low SF levels during the second trimester. Iron supplementation during pregnancy should be administered judiciously based on blood glucose level and iron storage capacity to maintain the SF level within an appropriate range.

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Keywords Gestational diabetes mellitus, Serum ferritin, Restricted cubic spline, Hemoglobin A1c

Background

Gestational diabetes mellitus (GDM) is characterized as abnormal glucose metabolism that is first identified during pregnancy. The worldwide incidence rate of this condition is around 14%, with certain regions seeing rates as high as 40% [1]. GDM may not only raise the occurrence of adverse perinatal outcomes such as preterm birth, shoulder dystocia, macrosomia, and hypertensive disorders during pregnancy, but also contribute to the poor long-term health of pregnant women and their children [1–4]. At present, the specific mechanism of the pathogenesis of GDM remains unclear, and there are also some constraints in the therapeutic management and prevention of this condition in clinics [5].

Recently, there have been consistent studies suggesting a specific association between iron storage and supplementation during pregnancy and the possibility of developing GDM. Among them, the relationship between ferritin levels and GDM risk has received the most extensive attention [6]. Ferritin is the best indicator to reflect the status of iron storage in the body, and a low level of serum ferritin (SF) is seen as a clinical indication of inadequate iron storage [7, 8]. The comprehensive analysis conducted by Li et al. [6] demonstrated that almost all relevant studies conducted in the last two decades have shown that excessive SF level was closely related to the increased risk of GDM. Evidently, an over accumulation of iron in the body might potentially facilitate the GDM development.

Concurrently, iron is an essential element for the growth and development of the fetus as well as the regeneration and proliferation of maternal red blood cells. Insufficient iron levels may result in maternal anemia, as well as increased risks for preterm birth, low birth weight, and even perinatal mortality [9]. At present, guidelines in various countries recommend maintaining a SF level of 30 ng/ml or more throughout pregnancy. Pregnant women with SF levels below this threshold are diagnosed with iron insufficiency and are advised to actively supplement iron [8, 10, 11].

Hence, it is crucial for pregnant women, particularly those without anemia (which often suggests improved nutritional condition and increased iron utilization), to maintain a reasonable iron storage status to prevent the development or advancement of GDM after fulfilling the iron needs of the mother and embryo during pregnancy. This aspect has not been examined in prior studies. In this study, we investigated the precise relationship between SF levels in the second and third trimesters and the development of GDM in non-anemic pregnant women. The findings of this study will provide valuable guidance for non-anemic pregnant women on the appropriate iron intake during pregnancy.

Methods

Study design and participants

A cohort of pregnant women, who maintained standardized medical records at the Women's Hospital, Zhejiang University School of Medicine during June 2021 to July 2022, were chosen for this study. According to certain policies of the local health system, the gestational weeks for establishing medical records of chosen participants ranged from 23 to 28 weeks. Once medical records have been established, a set of blood tests were generally conducted for assessment, including the measurement of hemoglobin, SF, Hemoglobin A1c (HbA1c), and the measurement or review of oral glucose tolerance test (OGTT). The subjects of this study were non-anemic pregnant women. The primary criterion identified was that the whole-blood hemoglobin level, as recorded in medical records, should not be below 105 g/L [8, 10]. At the same time, to minimize the impact of pregnancy inflammation, infection, hypertensive diseases, and other factors on ferritin levels indicating iron storage [12], we deliberately omitted pregnant women with notable autoimmune disorders (such as antiphospholipid syndrome), carriers of pathogens or infected participants (such as hepatitis B virus carriers), and other potential abnormal conditions (such as chronic hypertension). Also, for avoiding the confounding factors on GDM, we omitted pregnant women with type 2 diabetes mellitus, polycystic ovary syndrome and disorders with abnormal thyroid hormone levels. Besides, women who before gestation had heart, liver or kidney disease or other severe complications, or any history of smoking or drug abuse were excluded. Figure 1 provides a comprehensive description of the selection procedure for the study subjects.

Diagnostic criteria for GDM

The *Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy*, published by the World Health Organization in 2013, was used to verify the presence of GDM [13]. Specifically, a 75 g OGTT was conducted at 24–28 weeks: fasting blood glucose ≥ 5.1 mmol/L, 1-hour post-glucose load plasma glucose (1-h PG) ≥ 10 mmol/L or 2-h PG ≥ 8.5 mmol/L. Following the exclusion of type 2 diabetes, if any of the three criteria mentioned above were present, the diagnosis was made as GDM.

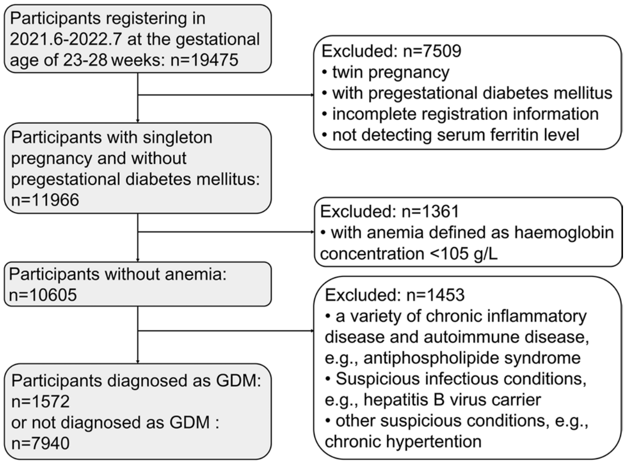

Fig. 1 Sample selection process flow chart. From participants registering during the time from June 2021 to July 2022 at the gestational age of 23–28 weeks, this study selected a final sample of 9,512 participants based specific criteria

Collection of variable-related information

Following the determination of the study subjects, pertinent data on the pregnant women was gathered from the hospital medical database. This included SF level, HbA1c level, hemoglobin level, OGTT results, age at conception, method of conception, pre-pregnancy body mass index, parity, family history of diabetes and education level. Methods for determining key indicators: 5 ml cubital venous blood was collected in the morning when OGTT was performed or within one week before OGTT timing during 23 to 28 weeks of gestation, and serum was separated by centrifugation. In accordance with the instructions provided by Abbott Laboratories, USA, the analysis of SF was performed utilizing the ARCHITECT i4000SR fully automated chemiluminescence immunoanalyzer and its accompanying reagents. The level of glucose was determined by the hexokinase method in the Beckman Coulter AU5800 automatic biochemical analyzer. The glycated hemoglobin was analyzed in venous blood, taken with vacutainer, containing K2EDTA as anticoagulant. The concentration was determined using the Tosoh HLC-723G8, which is based on the principle of high performance liquid chromatography.

Statistical analysis

The statistical analysis and charting of data were conducted using R (version 4.4.0; R Core Team, Vienna, Austria) and Stata (version 16; StataCorp LLC, College Station, TX, USA) statistical software. Kolmogorov-Smirnov test and qq plot were used to ascertain that all of the measurement data exhibited skewed distributions. Therefore, they were represented by median and interquartile range. The Mann-Whitney U test was used to assess the disparities in measurement data between the two groups of pregnant women, and chi-square analysis was used to compare the differences in enumeration data between the two groups. Restricted cubic splines were used to explore the relationship between GDM and blood glucose-related indicators and SF. In these studies, we performed natural logarithm transformation on SF levels to make them follow a normal distribution. In order to prevent outliers from exerting undue impact on the study results, a 1% winsorizing technique was used simultaneously. Statistical significance was defined as two-tailed $P < 0.05$.

Results

Clinical characteristics of GDM or non-GDM participants

A total of 1,572 GDM women and 7,940 non-GDM women were selected. The comparative analysis revealed that there were not only significant differences in HbA1c level and glucose levels during the OGTT in the second trimester between the two groups, but also obvious statistical differences in age at conception, education level, pre-pregnancy BMI, conception method, parity, hemoglobin level and family history of diabetes ($P < 0.05$ for all). Regarding ferritin, the SF level in the second trimester of the GDM group was significantly higher than that of the non-GDM group ($P = 0.017$), however, the magnitude of the difference between the two groups was not substantial (Table 1).

The association between serum SF levels and GDM risk development in the second trimester

Given the skewed distribution of SF levels in the study subjects, we used a natural logarithm transformation to analyze and display the relationship between GDM risk and SF levels. A nonlinear association was observed between the GDM risk and the SF levels during the second trimester ($P = 0.009$ for nonlinearity), characterized by an approximately U-shaped curve (Fig. 2). That is, as the SF levels increased, the probability of developing GDM decreased slightly. Until a certain threshold was met, the probability of developing GDM steadily rise as the SF levels increased, this threshold was notably below 30 ng/ml, which is the threshold suggesting iron supplement.

The relationships between blood glucose related indicators and SF levels during the second trimester of pregnancy

We stratified the pregnant women based on their diagnosis of GDM in order to further investigate the relationships between blood glucose related indicators and SF levels. The study revealed that the relationship between 1-h PG in OGTT and SF levels and between HbA1c and SF levels were different in the two groups. More precisely, in the group of GDM women, their 1-h PG showed a rising tendency as the SF level increased, seemed to

Table 1 Characteristics of the GDM group and non-GDM group

Characteristics	Non-GDM (*n* = 6,940)	GDM (*n* = 1,572)	*P*
Serum ferritin level			
Absolute level (ng/ml)	19.8 (12.9, 30.5)	20.5 (13.3, 32.3)	0.017
Relative level			0.001
< 30 ng/ml (%)	61.9	11.6	
≥ 30 ng/ml (%)	21.6	4.9	
Gestational age at detecting day (day)	173.1 (169.3, 178.6)	173.4 (169.2, 179.2)	0.490
Age when conceiving			< 0.001
< 25 years old (%)	5.09	0.3	
25 ~ < 35 years old (%)	68.1	12.5	
≥ 35 years old (%)	10.3	3.7	
Educational level			0.002
Lower than college (%)	8.7	2.1	
College (%)	59.7	12.0	
Higher than college (%)	15.0	2.4	
Pre-pregnancy body mass index (kg/m^2)			< 0.001
< 18.5 (%)	9.4	1.3	
18.5 ~ < 24 (%)	63.2	11.5	
24 ~ < 28 (%)	9.4	2.8	
≥ 28 (%)	1.5	0.9	
Parity			< 0.001
Primipara (%)	59.1	10.5	
Multipara (%)	24.4	6.1	
Parent with diabetes history			< 0.001
Yes (%)	82.3	16.1	
No (%)	1.1	0.5	
Mode of conception			< 0.001
Assisted conception (%)	77.7	14.9	
Natural conception (%)	5.8	1.7	
Hemoglobin level (g/L)			< 0.001
105 ~ < 110	13.3	2.2	
105 ~ < 120	41.9	7.6	
≥ 120	28.2	6.7	
HbA1c level (%)[ζ]	5.1 (5.0, 5.3)	5.4 (5.1, 5.6)	< 0.001
Results of OGTT[ɳ]			
FPG (mmol/L)	4.3 (4.1, 4.5)	4.5 (4.2, 4.8)	< 0.001
1-h PG (mmol/L)	7.5 (6.5, 8.4)	10.1 (9.3 10.7)	< 0.001
2-h PG (mmol/L)	6.6 (5.9, 7.3)	8.9 (8.4, 9.6)	< 0.001

[ζ]HbA1c level was simultaneously detected when the blood sampling was performed for detecting the level of ferritin at the gestational age of 23–28 weeks, with 165 participants' information missing

[ɳ]The 75-gram OGTT was regularly performed at the age of 24–28 weeks, and there were 6,052, 178 and 6,138 participants missing information of FPG, 1-h PG and 2-h PG, respectively

The statistical analyses on HbA1c level and OGTT parameters were performed with existing data, that is, participants with missing data were excluded when performing these analyses

GDM, gestational diabetes mellitus; HbA1c, glycated hemoglobin A1c; OGTT, oral glucose tolerance test; FPG, fasting plasma glucose; 1-h PG, one-hour post-load plasma glucose; 2-h PG, two-hour post-load plasma glucose

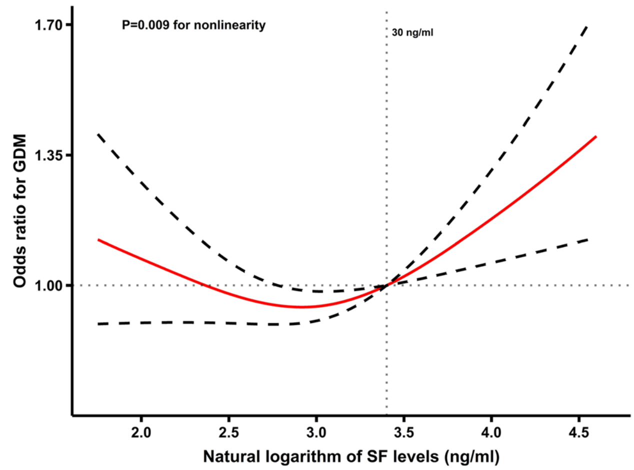

Fig. 2 Nonlinear association between GDM risks and SF levels during the second trimester. With the method of restricted cubic spline, odds ratios (red solid line) and 95% confidence intervals (black dashed lines) were calculated with a SF level of 30 ng/ml (vertical dotted line, 3.40 as the logarithmic value) as the reference, adjusted for age when conceiving, educational level, pre-pregnancy body mass index, parity, parent with diabetes history, mode of conception and hemoglobin level. A transformation of natural logarithm on serum ferritin level was performed to present a normal distribution. GDM, gestational diabetes mellitus; SF, serum ferritin

exhibit a linear pattern ($P = 0.748$ for nonlinearity). However, non-GDM women had little changes in their 1-h PG levels as the SF level increased, with the exception of minor variations. The correlation between the two factors exhibited a somewhat bell-shaped pattern ($P = 0.045$ for nonlinearity) (Fig. 3). The study findings on the relationship between HbA1c and SF level during the second trimester surpassed our first expectations. A strong negative relationship was seen between the HbA1c level and SF level in both groups when the SF level was below 30 ng/ml. However, a significant difference was seen when the SF level exceeded 30 ng/ml: the HbA1c level in non-GDM group showed no change with changes in SF level ($P < 0.001$ for nonlinearity), while the HbA1c level of GDM pregnant women slightly increased with increases in SF levels ($P < 0.001$ for nonlinearity) (Fig. 4).

The relationship between changes in HbA1c level and SF level during the third trimester

In order to investigate the relationship between the progression of GDM and the SF levels, we also examined the relationship between the variation of HbA1c levels throughout the third trimester and the fluctuation of SF levels. Due to its simplicity in measurement, HbA1c is the most reliable indicator for assessing blood glucose management [14]. According to whether GDM was diagnosed and the SF levels was less than 30 ng/ml during the second trimester, we categorized pregnant women who had rechecked HbA1c during the third trimester into four groups: the non-GDM low SF group, the GDM low

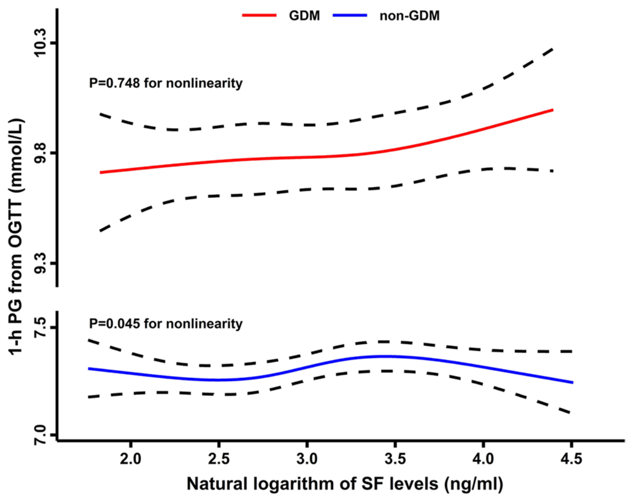

Fig. 3 Nonlinear associations between 1-h PG from OGTT and SF levels during the second trimester among participants with and without GDM. In the analyses of restricted cubic spline, the red solid line indicated the association among participants with GDM, the blue solid line indicated the association among participants without GDM, and the dashed lines indicated 95% confidence intervals. Models were adjusted for age when conceiving, educational level, pre-pregnancy body mass index, parity, parent with diabetes history, mode of conception and hemoglobin level. A transformation of natural logarithm on ferritin level was performed to present a normal distribution. 1-h PG, one-hour post-load plasma glucose; OGTT, oral glucose tolerance test; GDM, gestational diabetes mellitus; SF, serum ferritin

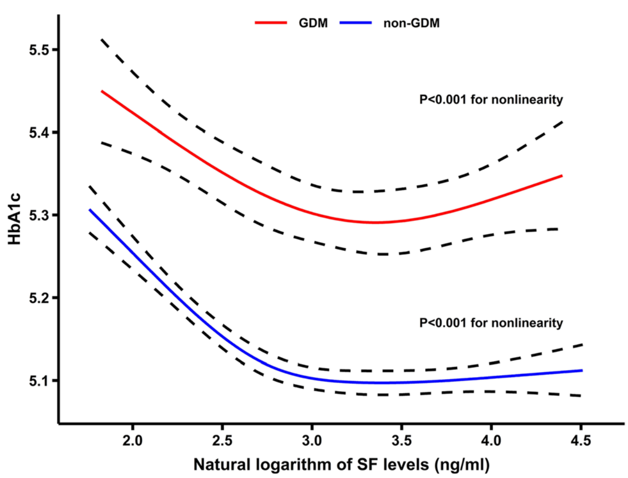

Fig. 4 Nonlinear associations between HbA1c levels and SF levels during the second trimester among participants with and without GDM. In the analyses of restricted cubic spline, the red solid line indicated the association among participants with GDM, the blue solid line indicated the association among participants without GDM, and the dashed lines indicated 95% confidence intervals. Models were adjusted for age when conceiving, educational level, pre-pregnancy body mass index, parity, parent with diabetes history, mode of conception and hemoglobin level. A transformation of natural logarithm on ferritin level was performed to present a normal distribution. HbA1c, glycated hemoglobin A1c; GDM, gestational diabetes mellitus; SF, serum ferritin

SF group, the non-GDM high SF group and the GDM high SF group. The changes in HbA1c and SF levels of each group were shown in Table S1. It should be noted that the gestational ages of the pregnant women for rechecking relevant indicators were not homogeneous. Consequently, we conducted average processing on their level variations during the analysis. To approximate the clinical frequency of prenatal checkups, we established the study variables as the average level changes occurring every 4 weeks (28 days). In general, pregnant women with a comparatively low SF levels during the second trimester had an increasing pattern throughout the third trimester. For pregnant women with a relatively high SF level, there was a downward trend in the third trimester. This may be related to the recommendations outlined in clinical guidelines for iron supplementation. However, the levels of HbA1c exhibited a rising pattern during the third trimester.

These four groups displayed significant heterogeneity in the relationship between the increase rate of HbA1c and the change of SF levels. When women without GDM or with low SF levels during the second trimester experienced a positive rise in SF levels during the third trimester, the increase in HbA1c levels showed a declining trend, particularly in the non-GDM low SF group. For the GDM high SF group, the relationship between the two indexes variation was more complex. Following the first positive rise in SF levels, the growth rate of HbA1c levels stayed almost constant, then progressively declined and ultimately increased. When the change in SF levels was around −2.5 ng/ml every 4 weeks, the rate of increase in HbA1c levels was seen to be the least significant ($P < 0.001$ for nonlinearity) (Fig. 5).

Discussion

This study primarily investigated the relationship between GDM and blood glucose-related indicators and SF levels in pregnant women without anemia throughout the second and third trimesters. It was found that the relationship between the GDM risk and SF levels exhibited a roughly U-shaped pattern. Furthermore, the relationship between blood glucose-related indicators and SF levels during the second trimester was not consistent between the GDM group and the non-GDM group. Concurrently, we observed that when the SF levels increased or decreased during the third trimester, the rise rate of HbA1c levels presented a slowdown trend. However, in women with GDM and a high SF level during the second trimester, if the SF level was kept in a high level during the third trimester, the increase rate of HbA1c level demonstrated an accelerated trend.

At present, it is well accepted that after excluding infection and inflammation, excessive SF is a manifestation of iron overload, and the latter significantly contributes

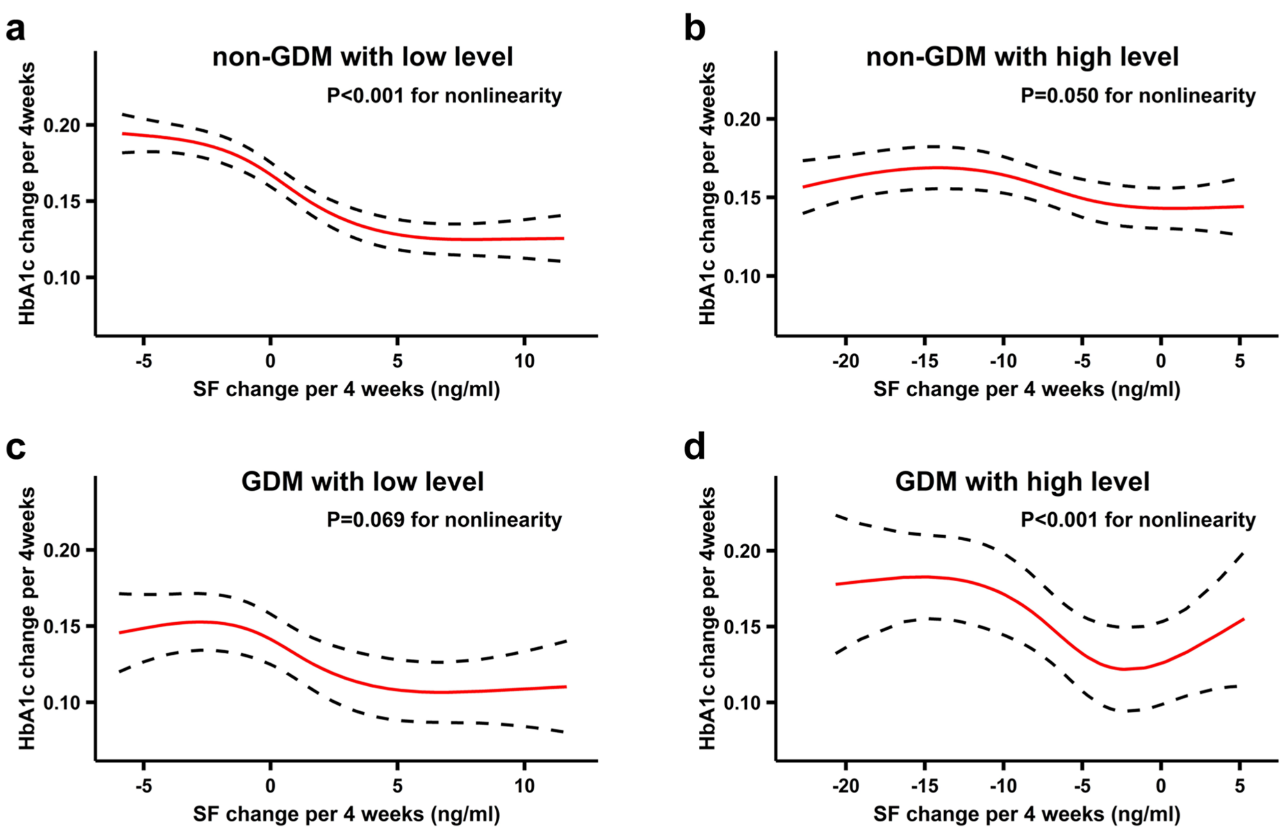

Fig. 5 Associations between the variation of HbA1c levels and the fluctuation of SF levels throughout the third trimester among participants stratified by GDM and SF level at the gestational age of 23–28 weeks. After GDM and non-GDM were confirmed with OGTT method, the second detecting of HbA1c level change and serum ferritin level always occurred in the third trimester, the associations between changes of the two parameters were explored using the analyses of restricted cubic splines among participants without GDM but low level of serum ferritin (**a**), participants without GDM but high level of serum ferritin (**b**), participants with GDM and low level of serum ferritin (**c**) and participants with GDM and high level of serum ferritin (**d**) detecting at the gestational age of 23–28 weeks, with 30 ng/ml as the cut-off. The red solid line indicated the predicted HbA1c change according to the ferritin fluctuation and the dashed lines indicated 95% confidence intervals. An average processing was conducted on the level variations during the analysis, that is, the variations were processed as the average level changes occurring every 4 weeks (28 days), to approximate the clinical frequency of prenatal visits. Models were adjusted for age when conceiving, educational level, pre-pregnancy body mass index, parity, parent with diabetes history, mode of conception and hemoglobin level. HbA1c, glycated hemoglobin A1c; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; SF, serum ferritin

to oxidative stress, decreased islet β function, insulin resistance and the development of diabetes [6, 15]. Our investigation revealed a positive correlation between the SF levels and the GDM risk, congruent with previous studies. However, in this study, the SF levels at which the increasing trend of GDM risk began to appear were lower than 30 ng/ml, which was roughly 17 ng/ml. In accordance with both local and international guidelines, a pregnant woman will get a diagnosis of iron deficiency if her SF level during the second trimester falls within the range of 17 to 30 ng/ml [8, 10, 11]. Under this situation, using iron supplements to raise her SF level to 30 ng/ml may heighten her potential to developing GDM. This issue bears merit to thorough investigation.

In addition, our findings indicated a strong correlation between an excessively low SF levels and a higher GDM risk during the second trimester. Furthermore, there existed a clear negative relationship between an exceptionally low SF level and an excessively high HbA1c level. These findings suggest that iron deficiency can also lead to abnormal glucose metabolism. The GDM risk generally showed a “U-shaped” relationship with the iron levels in the body. Actually, additional studies have also demonstrated that insufficient iron levels in the body or inadequate iron consumption heightened the GDM risk. The prospective research conducted by Zhu et al. [16] showed that a low serum iron level during early pregnancy might be associated with an elevated GDM risk in the later stages. The study undertaken by Wang et al. [17] using the UK Biobank database revealed that inadequate consumption of dietary iron was linked to a significant rise in the risk of developing type 2 diabetes. Furthermore, both investigations observed a U-shaped correlation between diabetes and the body iron level or intake. In fact, iron serves as a vital component not only for cell division and hemoglobin synthesis, but also for the regular functioning of cell mitochondria, oxidative stress response, and the proper insulin response to blood sugar levels [15, 16, 18]. Therefore, it is evident that iron insufficiency may lead to aberrant glucose metabolism and consequently different forms of diabetes. On the other hand, the inverse relationship between HbA1c and SF levels may be elucidated by the stated hypothesis. However, other studies have also shown that this inverse relationship may possibly be associated with the alteration of the quaternary structure of hemoglobin in cases of iron deficiency and the reduction in the renewal rate of red blood cells, therefore facilitating the glycosylation of the hemoglobin in circulation [18, 19].

The relationship between SF levels and the onset of GDM might not be a simple causal relationship, or the onset of GDM was not exclusively influenced by SF levels. Our stratified analysis of the relationship between blood glucose-related indicators and SF levels revealed that, even at the same SF levels, the blood glucose-related indicators of GDM and non-GDM pregnant women exhibited inconsistencies. Furthermore, the dynamic patterns of these indicators were also not consistent. As an illustration, 1-h PG of OGTT conducted at 24–28 weeks showed minimal variation in the 1-hour PG among non-GDM pregnant women as the SF levels increased. However, there was a clear tendency of positive linear relationship between these two indicators in GDM pregnant women. Comparatively, GDM pregnant women not only had a higher HbA1c level (at the same SF levels), but also exhibited an increasing trend in HbA1c levels as the SF levels exceeded 30 ng/ml. This trend was clearly different from that of non-GDM pregnant women, who essentially remained unchanged. Although our study has employed statistical methods to mitigate the impact of other factors, the results unequivocally indicated the presence of numerous additional factors or intricate processes implicated in the interaction between iron and the occurrence and development of GDM.

Currently, it is widely advised to provide active iron supplementation when the SF level is below 30ng/ml during pregnancy, both domestically and internationally. This recommendation is also applicable at our hospital. Therefore, it can be seen that the average SF level after four weeks generally increases for low SF levels during the second trimester. Conversely, for high SF levels in the same trimester, the opposite pattern emerges. Over the course of pregnancy, the level of insulin resistance and blood glucose will consistently rise [20]. All four groups of pregnant women in this study displayed an increasing tendency in their HbA1c levels throughout the third trimester, which aligns with this prediction. However, the rate at which HbA1c levels increased and the fluctuations in these values across the four groups were not uniform. More precisely, when SF levels were assessed during the second trimester, a more gradual decline in the high SF levels or a more rapid rise in the low SF levels would lead to a slower rise in HbA1c, particularly in non-GDM pregnant women with lower SF levels. The observed phenomenon may be attributed to the very consistent mechanism of glucose metabolism and hemoglobin glycation when the body maintains an adequate iron level [16–19]. However, when the SF level of pregnant women with GDM was very high during the second trimester, and thereafter there was no apparent decline or even an upward trajectory in SF level, the rate of HbA1c progression had an upward trend. One recent research reported a similar phenomenon: women with consistently high SF levels in the first and second trimesters had higher risks of GDM [21]. Therefore, the persistent high iron storage condition was directly linked to the aberrant decline in glucose metabolism. By combining the variations in HbA1c levels among the four groups of pregnant women together with the changes in SF levels, it appears that we could deduce the following conclusion: As pregnancy advances in the second and third trimesters, the unstable glucose metabolism and elevated iron levels in the body might lead to deteriorating blood glucose control. In light of the results of this study, it is recommended that pregnant women with low SF levels opt for active iron supplementation throughout the first and second trimester. However, in cases where there are significant risk factors for diabetes or prediabetes and the body's iron storage is relatively high, it is advisable to take caution while considering iron supplementation. This may explain why previous studies have drawn different conclusions when exploring whether iron supplementation will increase the risk of GDM [22]. The impact or potential hazards of iron supplementation on glucose metabolism may vary across pregnant women with different basic conditions and different baseline levels of iron storage.

An advantageous aspect of this study is the selection of non-anemic pregnant women as the study subjects, who were likely to have high levels of health and nutritional status. Concurrently, we eliminated pregnant women presenting with autoimmune disorders, infections, and other variables that raised suspicion. The number of relevant factors that may influence the relationship between SF levels and GDM is expected to be somewhat low. Secondly, we selected restricted cubic splines as a method of statistical analysis to maximally expose the non-linear relationship between the two variables. The identified "U"-shaped association might explain the contradictory findings of earlier conventional group comparison studies [6]. Thirdly, our study sample size was large enough to minimize the test errors.

This study also has certain limitations. First of all, this study was not a prospective cohort study and was unable to elucidate the causal relationship between SF levels and the occurrence and development of GDM. It is widely accepted that a prospective study with a substantial sample size and a more rational design in the subsequent phase might provide more robust and compelling findings. Secondly, this was a retrospective study, and although the study population and statistical methods had been optimized as much as possible, there were still some research biases. Simultaneously, there was a significant amount of missing data, including a large number of OGTT fasting blood glucose data and a small number of 1-h PG data and HbA1c data. Thirdly, it is important to note that while SF and HbA1c, the two research indicators chosen in this study, were highly accessible and reliable indicators of iron storage and blood glucose control in the body, they did not completely represent the corresponding real status in the body. Therefore, it is crucial to be more cautious when interpreting and implementing the findings of this study.

Conclusions

This study investigated the relationship between the SF levels and the occurrence and development of GDM in non-anemic pregnant women throughout late pregnancy. It was found that the extreme SF levels during the second trimester were associated with the incidence of GDM. If GDM pregnant women maintained high SF levels during the third trimester, the rate of HbA1c rise would exhibit an upward trend. During pregnancy, iron supplements should be dosed judiciously based on blood glucose status and iron storage capacity to maintain the SF levels within an appropriate range.

Abbreviations

1-h PG	One-hour post-load plasma glucose
2-h PG	Tow-hour post-load plasma glucose
BMI	Body mass index
FPG	Fasting plasma glucose
GDM	Gestational diabetes mellitus
HbA1c	Glycated hemoglobin A1c
OGTT	Oral glucose tolerance test
RCS	Restricted cubic spline
SF	Serum ferritin

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12884-025-07391-9.

Supplementary Material 1

Acknowledgements

Not applicable.

Author contributions

Menglin Zhou and Liying Song conceived the study. Menglin Zhou, Liying Song and Yan Huang analyzed data. Danqing Chen supervised the study. All authors were involved in writing the paper.

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Data availability

Data supporting the results of this study can be obtained on request to the author Menglin Zhou (marlin_zhou@zju.edu.cn).

Declarations

Ethics approval and consent to participate

The Medical Ethics Committee of Women's Hospital, Zhejiang University School of Medicine granted approval for this study (IRB-20240168-R). Given that this study was retrospective, the relevant data did not include the personal information of pregnant women and did not pose any threat to their economic interests or physiological well-being. Consequently, the Ethics Committee granted authority to waive the need for informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Hivert M, Backman H, Benhalima K, Catalano P, Desoye G, Immanuel J, et al. Pathophysiology from preconception, during pregnancy, and beyond. Lancet. 2024;404(10448):158–74. https://doi.org/10.1016/S0140-6736(24)00827-4.
2. Cosson E, Nachtergaele C, Vicaut E, Tatulashvili S, Sal M, Berkane N, et al. Metabolic characteristics and adverse pregnancy outcomes for women with hyperglycaemia in pregnancy as a function of insulin resistance. Diabetes Metab. 2022;48(3):101330. https://doi.org/10.1016/j.diabet.2022.101330.
3. Moon JH, Jang HC. Gestational diabetes mellitus: diagnostic approaches and maternal-offspring complications. Diabetes Metab J. 2022;46(1):3–14. https://doi.org/10.1016/j.diabet.2022.101330.
4. Okoth K, Chandan JS, Marshall T, Thangaratinam S, Thomas GN, Nirantharakumar K, et al. Association between the reproductive health of young women and cardiovascular disease in later life: umbrella review. BMJ. 2020;371:m3502. https://doi.org/10.1136/bmj.m3502.
5. Sweeting A, Hannah W, Backman H, Catalano P, Feghali M, Herman WH, et al. Epidemiology and management of gestational diabetes. Lancet. 2024;404(10448):175–92. https://doi.org/10.1016/S0140-6736(24)00825-0.
6. Li T, Zhang J, Li P. Ferritin and iron supplements in gestational diabetes mellitus: less or more? Eur J Nutr. 2024;63(1):67–78. https://doi.org/10.1007/s00394-023-03250-5.
7. Georgieff MK. Iron deficiency in pregnancy. Am J Obstet Gynecol. 2020;223(4):516–24. https://doi.org/10.1016/j.ajog.2020.03.006.
8. ACOG Committee. Anemia in pregnancy: ACOG practice bulletin, number 233. Obstet Gynecol. 2021;138(2):e55–64. https://doi.org/10.1097/AOG.0000000000004477.
9. Sangkhae V, Fisher AL, Ganz T, Nemeth E. Iron homeostasis during pregnancy: maternal, placental, and fetal regulatory mechanisms. Annu Rev Nutr. 2023;43:279–300. https://doi.org/10.1146/annurev-nutr-061021-030404.
10. Pavord S, Daru J, Prasannan N, Robinson S, Stanworth S, Girling J. UK guidelines on the management of iron deficiency in pregnancy. Brit J Haematol. 2020;188(6):819–30. https://doi.org/10.1111/bjh.16221.
11. Chinese Society of Perinatal Medicine. Guidelines for the diagnosis and treatment of iron deficiency and iron deficiency anemia during pregnancy. Chin J Perinat Med. 2014;17(7):451–4. https://doi.org/10.3760/cma.j.issn.1007-9408.2014.07.006. (in Chinese).

12. Chibanda Y, Brookes M, Churchill D, Al-Hassi H. The ferritin, Hepcidin and cytokines link in the diagnoses of iron deficiency anaemia during pregnancy: a review. Int J Mol Sci. 2023;24(17):13323. https://doi.org/10.3390/ijms241713323.
13. World Health Organization. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a world health organization guideline. Diabetes Res Clin Pract. 2014;103(3):341–63. https://doi.org/10.1016/j.diabres.2013.10.012.
14. Ceriello A, Monnier L, Owens D. Glycaemic variability in diabetes: clinical and therapeutic implications. Lancet Diabetes Endocrinol. 2019;7(3):221–30. https://doi.org/10.1016/S2213-8587(18)30136-0.
15. Harrison AV, Lorenzo FR, McClain DA. Iron and the pathophysiology of diabetes. Annu Rev Physiol. 2023;85:339–62. https://doi.org/10.1146/annurev-physiol-022522-102832.
16. Zhu B, Liang C, Xia X, Huang K, Yan S, Hao J, et al. Iron-related factors in early pregnancy and subsequent risk of gestational diabetes mellitus: the Ma'anshan birth cohort (MABC) study. Biol Trace Elem Res. 2019;191(1):45–53. https://doi.org/10.1007/s12011-018-1595-4.
17. Wang R, Liu Y, Thabane L, Olier I, Li L, Ortega-Martorell S, et al. Relationship between trajectories of dietary iron intake and risk of type 2 diabetes mellitus: evidence from a prospective cohort study. Nutr J. 2024;23(1):15. https://doi.org/10.1186/s12937-024-00925-5.
18. Guo W, Zhou Q, Jia Y, Xu J. Increased levels of glycated hemoglobin A1c and Iron deficiency anemia: A review. Med Sci Monit. 2019;25:8371–8. https://doi.org/10.12659/msm.916719.
19. Satriawibawa IWE, Arimbawa IM, Ariawati K, Suparyatha IBG, Putra IGNS, Hartawan INB. Serum iron is negatively correlated with the HbA1c level in children and adolescents with type 1 diabetes mellitus. Clin Pediatr Endocri. 2022;31(4):242–9. https://doi.org/10.1297/cpe.2022-0012.
20. McIntyre HD, Catalano P, Zhang C, Desoye G, Mathiesen ER, Damm P. Gestational diabetes mellitus. Nat Rev Dis Primers. 2019;5(1):47. https://doi.org/10.1038/s41572-019-0098-8.
21. Su S, Gao S, Zhang E, Liu J, Xie S, Zhang Y, et al. The association between serum ferritin levels and the risk of gestational diabetes mellitus: a prospective cohort study. BMC Pregnancy Childbirth. 2025;25(1):95. https://doi.org/10.1186/s12884-025-07220-z.
22. Petry CJ. Iron supplementation in pregnancy and risk of gestational diabetes: a narrative review. Nutrients. 2022;14(22):4791. https://doi.org/10.3390/nu14224791.

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