Original Article

Relationship between iron metabolism and gestational diabetes mellitus: A systemic review and meta analysis

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Background and Objectives: To investigate the relationship between serum iron metabolism indexes and gestational diabetes mellitus (GDM) using a meta-analysis. **Methods and Study Design:** Databases including PubMed, Web of Science, Embase, and Cochrane Library were searched. Prospective cohort or case-control studies evaluating the relationships between serum iron metabolism indexes and GDM were retrieved from these databases. The outcome indicators, such as mean ± standard deviation, relative risk (RR), or odds ratio (OR) were extracted. The RR or OR, standard mean difference (SMD), and 95% confidence interval (CI) were used to calculate the combined effect sizes. **Results:** A total of 32 studies on the relationships between serum iron metabolic indexes and GDM were included. The serum iron [SMD=0.40 mg/dL, 95% CI (0.16, 0.64), p=0.001], ferritin [SMD=0.58 ng/mL, 95% CI (0.35, 0.81), p<0.001], hemoglobin [SMD=0.48 g/dL, 95% CI (0.28, 0.67), p<0.001], transferrin saturation [SMD=0.83%, 95% CI (0.15, 1.52), p=0.000], and hepcidin [SMD=0.63 ng/mL, 95% CI (0.09, 1.18), p=0.023] levels were higher in the GDM group than in the non-GDM group, whereas total iron binding ability [SMD = -0.53 μg/dL, 95% CI (-1.05, -0.02), p=0.001] was lower in the GDM group than in the non-GDM group. High serum ferritin [OR=1.92, 95% CI (1.59, 2.32), p<0.001] and hemoglobin levels [OR=1.30, 95% CI (1.04,1.63), p=0.023] were associated with GDM risk. **Conclusions:** Serum iron, ferritin, transferrin saturation, hepcidin, and hemoglobin levels were higher and total iron binding ability was lower in GDM patients than in those without GDM. High serum ferritin and hemoglobin levels were associated with GDM risk.

Key Words: gestational diabetes mellitus, iron; ferritin, transferrin, transferrin saturation

INTRODUCTION

Gestational diabetes mellitus (GDM), a metabolic disorder common during pregnancy, refers to chronic hyperglycemia or abnormal glucose tolerance in women who have not previously been diagnosed with diabetes.[1] Epidemiological investigations have shown that the abnormal glucose tolerance of the majority of gestational diabetes patients usually returns to normal levels after childbirth, and the pathological manifestations caused by elevated blood glucose also disappear at the end of pregnancy; thus, it is defined as a self-healing disease.[2] In 2013, the International Diabetes Association evaluated the prevalence of GDM in pregnant women aged 20–49 years in 34 countries, and the prevalence of GDM was approximately 17.5–24% in the United Kingdom; 4.2–15.3% in Canada; 8.3–15.4% in Nigeria; 11–18% in Malaysia; and 5–10% in China, Spain, Turkey, and the United States.[3]

For humans, trace element iron is one of the essential metal elements participating in many physiological processes, such as oxygen transport, energy and hemoglobin production, DNA synthesis, redox reaction, and cellular respiration. Iron binds to the plasma transferrin and accumulates in the cell in the form of ferritin. Iron readily accepts and contributes electrons through conversion between Fe^{2+} and Fe^{3+}. The main source of iron is food, and the low pH of the gastric juice helps dissolve the ingested iron. The duodenal epithelial cells sense the body's need for iron and reduce Fe^{3+} to Fe^{2+} by the iron reductase cytochrome B at the top of the chorionic membrane in the small intestine. Then divalent metal transporter 1 (DMT1) transfers iron into the intestinal epithelial cells through the process of proton binding. Then, iron is transferred to the plasma for systemic transport through the basolateral membrane, while the other part of iron is directly stored in the cell in the form of ferritin.[4] Hepcidin is a cytokine induced antibacterial protein produced in the liver. Under physiological conditions, excess iron can promote the secretion of hepcidin through the binding of iron transporters to transferrin receptor 1 (TfR1) and transferrin receptor 2 (TfR2) on the membrane of hepatocytes.[4,5]

Injury in the islet β cells and insulin resistance are one of the main pathophysiological mechanisms of GDM. Iron is involved in the process of insulin secretion and is a

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transition metal with redox activity. Excess iron is potentially dangerous as it catalyzes cellular reactions and converts hydrogen peroxide into free radical ions to damage tissues. Then the free radical ions may attack cell membranes, proteins, and DNA, and interfere with insulin signal transduction, eventually leading to abnormal glucose metabolism.[6] The iron overload may induce insulin resistance by increasing the burden on the liver to reduce liver glycogen synthesis and weaken the sensitivity to insulin signals. Excessive iron leads to a decrease in glucose oxidative energy supply and enhanced fatty acid metabolism in skeletal muscle cells and reduces insulin-induced glucose transport in adipocytes. Iron overload is common in diabetes; however, iron consumption may have a protective effect on the development of diabetes.[7]

Although there are several studies on the relationship between iron metabolism and GDM, the results are not consistent, possibly due to the differences in the study population, sample sizes, and research design. In addition, no single serum iron biomarker can reflect the true iron status. The comprehensive analysis of various iron metabolism indices, such as iron, ferritin, hemoglobin (Hb), transferrin, transferrin saturation, soluble transferrin receptor, total iron binding capacity, and hepcidin, may be able to fully reflect the clinical situation; however, most of the included studies failed to measure all iron metabolism indices. The present study investigated the relationships between these serum iron metabolism indices and GDM using a meta-analysis and evaluated the predictive value of the indexes for GDM.

METHODS

Inclusion and exclusion criteria

Inclusion criteria

The inclusion criteria were as follows: (1) studies based on the human body; (2) studies on the relationships between iron metabolism indices, such as serum iron (SI), serum ferritin (SF), Hb, serum transferrin (Tf), serum transferrin saturation (TSAT), serum soluble transferrin receptor (sTfR), serum total iron binding capacity (TIBC), serum hepcidin, and GDM; (3) prospective cohort studies or case-control studies; and (4) the ability to calculate data, such as relative risk (RR), odds ratio (OR), and mean ± standard deviation (SD).

Exclusion criteria

The exclusion criteria were as follows: (1) Studies based on animals; (2) case reports, summaries, meetings, and reviews; (3) repeated studies; (4) data as OR or RR, standard mean difference (SMD) cannot be calculated; and (5) studies with incomplete data and poor quality.

Literature retrieval and quality evaluation

According to the meta-analysis method recommended by observational epidemiological studies, PubMed, Web of Science, Embase, and Cochrane Library were searched for the English studies on the relationships between serum iron metabolism indices (SI, SF, Hb, Tf, TSAT, sTfR, TIBC, and hepcidin) and GDM. The references of the retrieved documents were traced until September 2020. Two researchers independently screened the studies in accordance with the inclusion and exclusion criteria. If there was divergence, the inclusion was decided through discussion. For the studies whose inclusion could not be determined, a third person was consulted.

The search strategy in PubMed are as follows: ((“Iron”[Mesh]) OR (iron)) AND (((“Diabetes, Gestational”[Mesh]) OR ((((((Diabetes, Pregnancy-Induced) OR (Diabetes, Pregnancy Induced)) OR (Pregnancy-Induced Diabetes)) OR (Gestational Diabetes)) OR (Diabetes Mellitus, Gestational)) OR (GDM)) OR (Gestational Diabetes Mellitus))) OR ((gestational) AND (diabetes))). The search strategy in Embased are as follows: #1 ‘iron’/exp ; #2 ‘pregnancy diabetes mellitus’/exp ; #3 ‘diabetes, gestational’:ab,ti OR‘diabetes, pregnancy-induced’:ab,ti OR‘diabetes, pregnancy induced’:ab,ti OR‘pregnancy-induced diabetes’:ab,ti OR‘gestational diabetes’:ab,ti OR‘diabetes mellitus, gestational’:ab,ti OR‘gestational diabetes mellitus’:ab,ti OR‘GDM’:ab,ti ; #4 #2 OR #3 ; #5 #1 AND #4

The quality of the included literature was assessed based on the Newcastle Ottawa Scale (NOS) of the case-control study or cohort studies. If the NOS score was ≥5, the study was considered to be of high quality.

Publication bias was detected using Begg’s and Egger’s tests. When the p value of Begg’s and Egger’s test was >0.05, it indicated that there was less publication bias in the included study. All data were analyzed using the Stata 15.1 software.

Data extraction

We gathered the following information from the included studies: the first author’s name, year of publication, country in which the study was conducted, average age, number of GDM patients, total study population, gestational stage of GDM patients at the time of blood collection, outcome indicators of each index such as mean, SD, estimated RR or OR, 95% confidence interval (CI), and adjusted parameters.

Statistical analysis

For these indicators such as SI, SF, Hb, TIBC, Tf, sTfR, TSAT, hepcidin, mean and SD were extracted, and SMD was considered as the effect size. When the effect size was equal to 0 or its 95% CI included 0, the diamond box representing the combined effect size in the forest plot intersected with the equivalent line, indicating that there was no statistically significant difference for the outcome indicators between the GDM and non-GDM groups. When the effect size was greater than 0 and the lower limit of 95% CI was greater than 0, the rhombus box in the forest map was on the right side of the equivalent line, indicating that the outcome index level was higher than in the GDM group in the non-GDM group. When the effect size was less than 0 and the upper limit of 95% CI was less than 0, the diamond box in the forest plot was on the left side of the equivalent line, indicating that the outcome index level was lower in the GDM group than in the non-GDM group.

For the risks between SF, Hb, and GDM, the OR or RR were extracted and the simplex effect size and 95% CI was combined. When the effect size was equal to 1 or its 95% CI included 1, the diamond box representing the combined effect size in the forest map intersected the

equivalent line, indicating that the outcome index was not correlated with the risk of GDM. When the effect size was greater than 1 and the lower limit of 95% CI was greater than 1, the diamond box in the forest map was on the right side of the equivalent line, indicating that the outcome index was positively correlated with the risk of GDM. When the effect size was less than 1 and the upper limit of 95% CI was less than 1, the diamond box in the forest map was on the left side of the equivalent line, indicating that the outcome index was negatively correlated with the risk of GDM. The test level of meta-analysis was set as α=0.05.

Heterogeneity test and subgroup analysis

The heterogeneity among the included studies was determined using the chi-square test (test level set as α=0.1). If p>0.1, $I^2 \leq 50\%$, the heterogeneity was small, and a fixed-effect model was selected for meta-analysis. If p<0.1, I^2>50%, indicated statistical heterogeneity, the random effects model was selected for meta-analysis.

If there was significant heterogeneity among study results, subgroup analysis was performed to observe the results after eliminating the influence of confounding factors, such as region, age, total number of study participants, detection methods of outcome indicators, and the gestational stage of the GDM patients at the time of blood collection.

RESULTS

Screening literature results

A total of 1,100 studies were obtained through preliminary computer retrieval, including 378 studies in PubMed, 336 in Web of Science, 317 in Embase, and 69 in Cochrane Library. All references were imported into ENdnote X9, and 328 duplicate references were excluded. After reading the titles and abstracts, 665 articles were screened out, including 167 reviews, 12 meta-analyses, 8 comments and conferences, 41 animal experiments, and 437 irrelevant studies. After careful reading of the full text of the remaining 107 articles, 75 articles were removed, including 15 articles inconsistent outcome indicators, 3 articles with duplicate report results, 27 articles whose original text was not available, and 30 articles with inconsistent content. Finally, 32 studies were included.[8-39] The screening process is shown in Figure 1.

Basic features of the included studies

The 32 selected articles were carefully read and the relevant data was extracted for each study. The data included the first author's name, year of publication, the country in which the study was conducted, average age, number of GDM and non-GDM groups, the total number of study population, and the gestational stage of GDM patients at the time of blood collection [early pregnancy (T1): <14 gestation weeks; second trimester (T2): ≥14 gestation weeks and <28 gestation weeks; third trimester (T3): ≥28 gestation weeks)], different SF and Hb level groups (low-level and high- level groups), mean ± SD, RR or OR and 95% CI of outcome indicators, and adjusted parameters. The basic characteristics of the included literatures are shown in Table 1.

The quality of the included studies was assessed using the NOS scale. Case-control studies scored 6–8 and cohort studies scored 6–9, both of which were of high quality. The Begg's and Egger's tests showed that except for SF and Hb, the p value of the other indices were greater than 0.05 (Table 2). This suggests a less possibility of publication bias.

Comparison of the serum iron metabolism indices levels between the GDM and non-GDM groups

There were 12 studies on the difference in SI levels,[11-14,16,18-20,29,35,38-39] 15 studies on the difference in SF levels,[11-14,20-22,25-27,29,31-32,34,39] 16 studies on the difference in

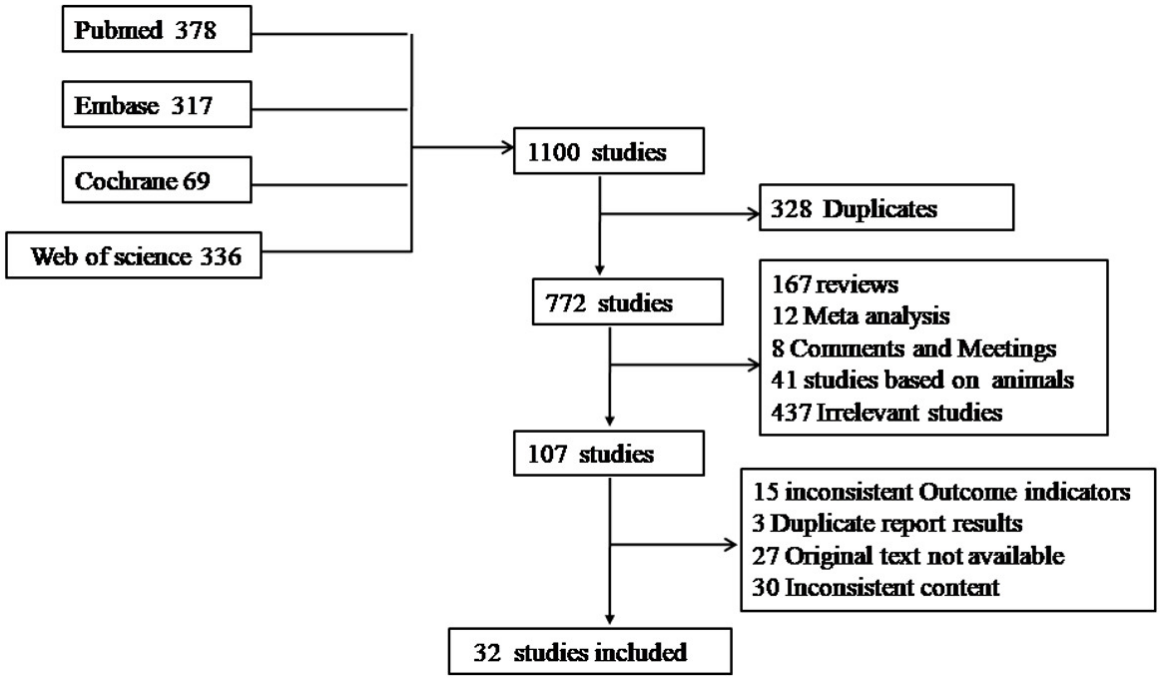

Figure 1. The screening process of the literatures.

Table 1. The basic characteristics of the included literatures

First Author	Country	Study type	N	GDM/ non-GDM number	Gestational stage	Average age	Index included	Hb (Low/High level groups)	SF (Low/High level groups)	Adjusted parameters
Lao[15] (2001)	China	Cohort	291	97/194	T3	32.5	SI/SF/Hb/Tf/TSAT	-	-	-
Lao[24] (2002)	China	Cohort	730	94/636	T3	29.7	Hb	<11.5 g/dL *vs* >13.0 g/dL		BMI
Wang[18] (2002)	China	Case-control	136	46/90	-	-	SI	-	-	-
Al-Saleh[19] (2004)	Kuwait	Case-control	30	15/15	T3	29	SI	-	-	-
Tarim[22] (2004)	Turkey	Cohort	253	20/233	T1	27.1	Hb/SF	-	-	-
Chen[28] (2006)	USA	Cohort	1456	45/1411	T2	22.14	Hb/SF	<13 g/dL vs >13.0 g/dL	<35.19 ng/mL *vs* ≥35.63 ng/mL	Age
Al-Saleh[35] (2007)	Kuwait	Case-control	21	10/11	T3	30	SI	-	-	-
Afkhami[11] (2009)	Iran	Case-control	68	34/34	T2	-	SI/SF/Hb/TBIC/TSAT	-	-	-
Soubasi[8] (2010)	Greek	Cohort	63	6/57	T2	30.5	SF	-	≤60 ng/mL *vs* >60 ng/mL	
Sharifi[34] (2010)	Iran	Case-control	128	64/64	T3	30	Hb/SF	-	≤82.85 ng/mL *vs* >82.85 ng/mL	Pre-pregnancy BMI, gestational stage, race, family history of diabetes, parity, smoking history
Akhlaghi[16] (2012)	Iran	Case-control	60	30/30	T2	30	SI	-	-	-
Amiri[12] (2013)	Iran	Case-control	200	100/100	T2	25.69	SI/SF/TBIC	-	≤80 ng/mL *vs* >80 ng/mL	BMI
Baddour[29] (2013)	French Canadian	Case-control	60	15/45	T3	29.1	Hb/SF/sTfR	-	-	-
Behboudi[17] (2013)	Iran	Cohort	1033	72/961	T2	27.57	SI		-	-
Derbent[13] (2013)	Turkey	Case-control	102	30/72	T2	27.5	SI/SF/Hb/Tf/Hepcidin			
Kaygusuz[14] (2013)	Turkey	Case-control	58	30/28	T2	30	SI/SF/Hb/TBIC/TSAT			
Pan[33] (2013)	China	Case-control	713	243/470	24-32weeks	29.51	Hb			
Javadian[25] (2013)	Iran	Case-control	102	52/50	T2	31.24	SF/Hb			
Ozyer[32] (2014)	Trukey	Case-control	105	35/70	T2	29.2	SF	-	-	-
Zein[9] (2015)	Lebanon	Cohort	104	16/88	T2	26.46	SF/Hb	<12.5 g/dL vs >12.5 g/dL	<38.5 ng/mL vs ≥38.5 ng/mL	Age, pre-pregnancy BMI, gestational stage, family history of diabetes, CRP, FPG

N: the total number of study population; -: Not reported in the original literatures. BMI: Body mass index; CRP: C-reactive protein; FPG: fasting blood glucose; LDL-C: Low density lipoprotein cholesterol; TC: total cholesterol; Hb: Hemoglobin; SI: serum iron; SF: serum ferritin; TBIC: total iron binding force; Tf: Transferrin; sTfR: soluble transferrin receptor; TSAT: Transferrin saturation.

Table 1. The basic characteristics of the included literatures (cont.)

First Author	Country	Study type	N	GDM/ non-GDM number	Gestational stage	Average age	Index included	Hb (Low/High level groups)	SF (Low/High level groups)	Adjusted parameters
Bowers[31] (2016)	Danish	Case-control	699	350/349	T1	32.2	SF/sTfR	-	<25 ng/mL *vs* >141 ng/mL	Age, pre-pregnancy BMI, family history of diabetes, exercise during pregnancy, CRP and LDLC
Rawal[27] (2017)	USA	Cohort	321	107/214	T2	30.5	SF/Hepcidin/sTfR	-	<34.32 ng/mL *vs* >77.51 ng/mL	Age, pre-pregnancy BMI, gestational stage, family history of diabetes, parity, CRP, education
Soheilyhah[20] (2017)	Iran	Cohort	1358	300/1058	T1	-	SI/SF/Hb/TBIC	-	<45 ng/mL *vs* ≥45 ng/mL	-
ZhiguoWang[21] (2018)	China	Case-control	793	92/701	T2	30.59	Hb/SF	-	-	-
chen-Wang[36] (2018)	China	Case-control	21577	4337/17240	T1	29.8	Hb	<13 g/dL *vs* 13 g/dL	-	Age, BMI
Roverso[37] (2019)	Italy	Case-control	76	38/38	T3	33.4	SI	-	-	-
Zhu[38] (2018)	China	Cohort	3289	429/2860	T2	26.4	SI/Hb	Continuous numerical		Age, BMI, family history of diabetes, parity, smoking, alcohol consumption, gestational stage, income, education
Feng[39] (2020)	China	Case-control	150	75/75	T2	28.8	SI/SF/Hb/TSAT	-	-	-
Grunnet[26] (2020)	Tanzania,	Case-control	392	153/239	T3	27	Hb/SF	-	-	-
Rayis[23] (2020)	Sudan	Cohort	259	48/211	T2	28.02	Hb	≤10.8 g/dL *vs* 10.8 g/dL		-
Cheng[10] (2020)	China	Cohort	851	132/719	10-20weeks	30.16	SF	-	<35.9 ng/mL *vs* > 87.2 ng/mL	Age, pre-pregnancy BMI, gestational stage, family history of diabetes, parity, Hb, TC, LDL-C, history of polycystic ovary syndrome
SI[30] (2020)	China	Cohort	1128	223/905	T1	28.6	Hb	-	-	-

N: the total number of study population; -: Not reported in the original literatures. BMI: Body mass index; CRP: C-reactive protein; FPG: fasting blood glucose; LDL-C: Low density lipoprotein cholesterol; TC: total cholesterol; Hb: Hemoglobin; SI: serum iron; SF: serum ferritin; TBIC: total iron binding force; Tf: Transferrin; sTfR: soluble transferrin receptor; TSAT: Transferrin saturation.

Table 2. Summary of variance and bias test of serum iron metabolism index (SMD)

Index	Number of studies	Combined effect size SMD (95% CI)	Heterogeneity		Significance of the effect		Bias test	
			I^2 (%)	*p* value	z value	*p* value	Begg's	Egger's
SI								
a	12	0.40 (0.16, 0.64)	88.1	0.000	3.27	0.001	0.837	0.136
b	9	0.27 (0.18, 0.36)	35.9	0.131	5.58	<0.0001	1	0.524
SF								
a	15	0.58 (0.35, 0.81)	89.6	0.000	5.05	<0.0001	0.092	0.028
b	10	0.45 (0.35, 0.55)	26.2	0.203	8.89	<0.0001	0.721	0.292
Hb								
a	16	0.48 (0.28, 0.67)	94.4	0.000	4.78	<0.0001	0.022	0.135
b	8	0.34 (0.22, 0.46)	36.0	0.142	5.69	<0.0001	0.386	0.673
TBIC								
a	4	-0.53 (-1.05, -0.02)	90.5	0.000	3.47	0.001	0.308	0.290
b	3	-0.17 (-0.43, 0.09)	62.5	0.069	1.29	0.179	1	0.711
TSAT								
a	4	0.52 (0.35, 0.70)	92	0.000	2.37	0.018	0.308	0.251
b	3	0.36 (0.18, 0.55)	0	0.561	3.89	<0.0001	1	0.741
sTfR								
a	2	-0.08 (-0.66, 0.50)	73.8	0.051	0.27	0.787	-	-
Hepcidin								
a	2	0.63 (0.09, 1.18)	78.7	0.000	2.27	0.023	-	-

SI: serum iron; SF: serum ferritin; Hb: Hemoglobin; TBIC: total iron binding force; TSAT: Transferrin saturation;sTfR: soluble transferrin receptor.
[a]Meta-analysis of all literatures before sensitivity analysis.
[b]Meta-analysis of all literatures after sensitivity analysis.

Hb levels,[11,13-15,20-23,25-26,29,33,34,36,38-39] 4 studies on the difference in serum TIBC levels,[11,12,14,20] 4 studies between the difference in serum TSAT levels,[11,14,15,39] 2 studies on the difference in serum hepcidin levels,[13,27] and 2 studies on the difference in serum sTfR levels,[29,31] between the GDM and non-DM groups.

There was statistical heterogeneity among the results of each study, and the random effects model was selected for meta-analysis. The results showed that the SI concentration was significantly higher in the GDM group than in the non-GDM group (SMD=0.40 μg/dL, 95% CI [0.16, 0.64], *p*=0.001) (Figure 2A). SF concentration were significantly higher in the GDM group than in the non-GDM group (SMD=0.58 ng/mL, 95% CI [0.35, 0.81], *p*<0.0001) (Figure 2B). Hb concentration were significantly higher in the GDM group than in the non-GDM group (SMD=0.48 g/dL, 95% CI [0.28, 0.67], *p*<0.0001 (Figure 2C). Serum TIBC concentration were significantly lower in the GDM group than in the non-GDM group (SMD=-0.53 μg/dL, 95% CI [-1.05, -0.02], *p*= 0.001) (Figure 2D). Serum TSAT levels were higher in the GDM group than in the non-GDM group (SMD=0.83%, 95% CI [0.15, 1.52], *p*<0.0001) (Figure 2E). Serum hepcidin concentration were significantly higher in the GDM group than in the non-GDM group (SMD=0.63 ng/mL, 95% CI [0.09, 1.18], *p*=0.000) (Figure 2F). No significant difference was found in the serum sTfR concentration between the GDM and non-GDM groups (SMD=-0.08 mg/L, 95% CI [-0.66, 0.50], *p* =0.787) (Figure 2G).

As for the comparison of serum Tf levels between the GDM and non-GDM groups, two studies were retrieved.13,15 However, the data given in the literature could not be converted into mean ± SD; therefore, the meta-analysis was not performed.

Iron metabolism index concentration and the risk of GDM

A total of nine studies on SF and the risk of GDM were included.[8-10,12,20,27,28,31,34] According to the SF concentration of the included studies, they were divided into high-level and low-level SF groups (Table 1). Seven of the nine studies were adjusted for the parameters, as shown in Table 1. A meta-analysis was performed before and after parameter adjustment, and the low-level SF group was considered as the reference group (OR=1). Before the parameters are adjusted, the heterogeneity among the results is small (I^2=15.1%, *p*=0.308). The fixed-effect model was selected for meta-analysis, and the results showed that compared with the low-level SF group, the high-level SF group was associated with increased risk of GDM (OR=1.92, 95% CI [1.59, 2.32], *p*<0.0001) (Figure 3A). The seven studies included after parameter adjustment showed no significant heterogeneity (I^2=0%, *p*=0.953). A meta-analysis conducted using a fixed-effect model suggested that a high SF level was still significantly associated with the risk of GDM (OR=2.25, 95% CI [1.67,3.03], *p*<0.0001) (Figure 3A).

The studies on the risks of Hb and GDM were divided into low-level and high- level Hb groups according to the included studies (Table 1), and the low-level Hb group was used as the reference (OR=1). A total of six studies on the relationship between Hb and the risk of GDM were included,[9,23,24,28,36,38] one study of them only provided the OR value after adjusting parameters,[28] and the other two studies did not adjust parameters when analyzing the risk relationship between Hb and GDM.[9,23] Therefore, before adjusting the parameters, a total of five studies were included,[9,23,24,36,38] and there was statistical heterogeneity (I^2=89.8%, *p*<0.0001). The random effects model was applied and the results showed that compared with the low-level Hb group, the high-level Hb group was associ-

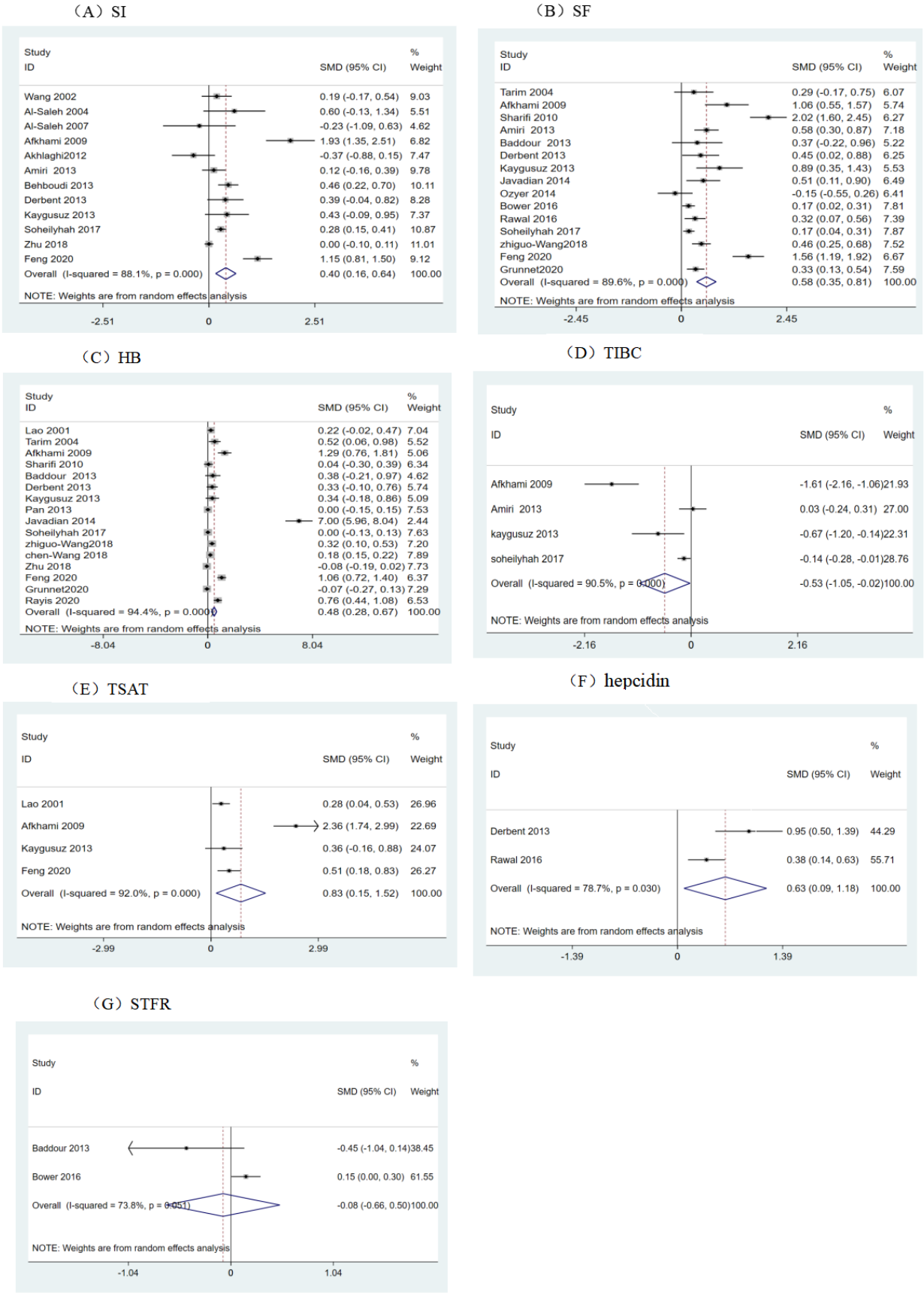

Figure 2. Comparison of the serum iron metabolism indices levels between the GDM and non-GDM groups. (A): serum iron (SI); (B): serum ferritin (SF); (C): hemoglobin (HB); (D): serum total iron binding capacity (TIBC); (E): serum transferrin saturation (TSAT); (F): hepcidin; (G): serum soluble transferrin receptor (STFR).

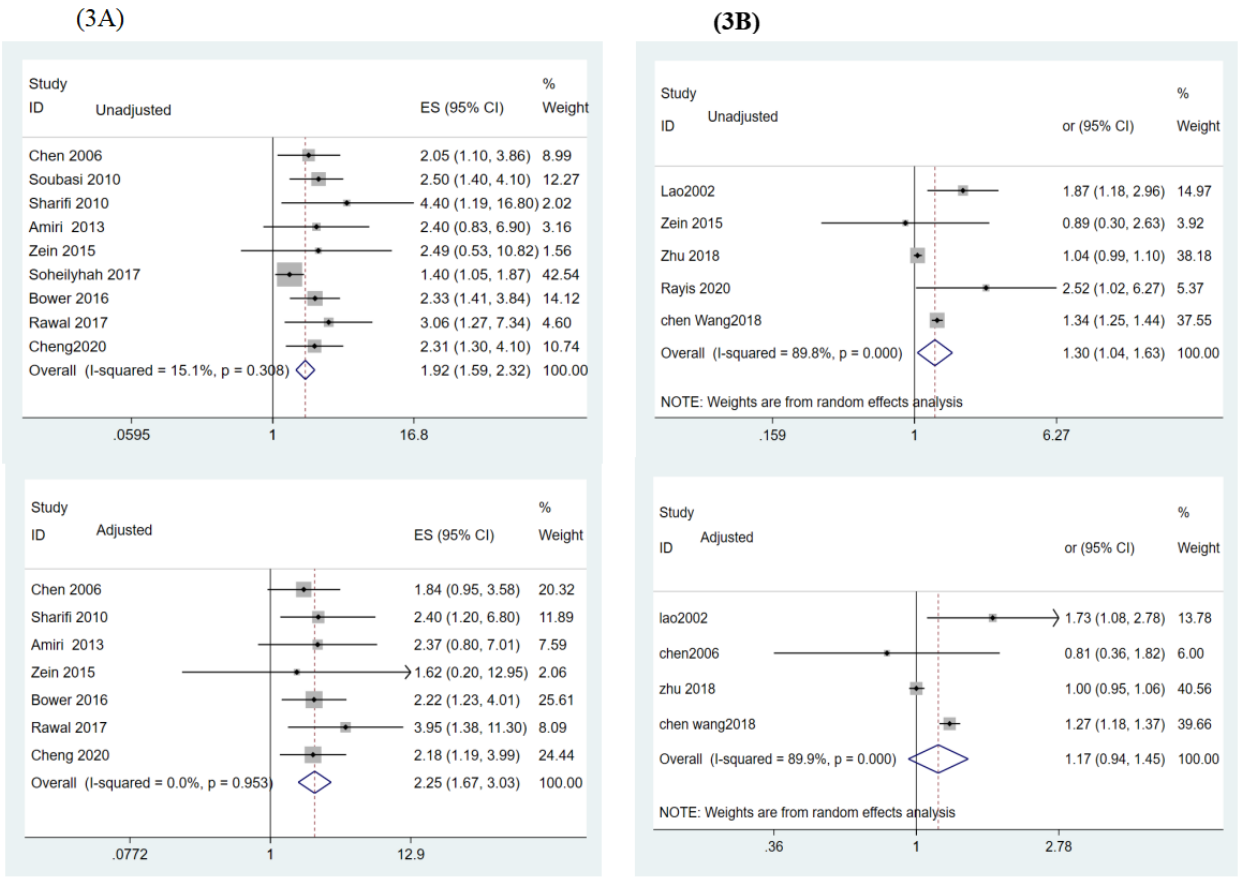

Figure 3. Serum ferritin and hemoglobin levels and the risk of GDM before and after parameter adjustment. (A): serum ferritin; (B): hemoglobin.

ated with an increased risk of GDM (OR=1.30, 95% CI [1.04, 1.63], p=0.023) (Figure 3B). After adjusting the parameters, a total of four studies were included.24,28,36,38 This indicated that Hb was not related to the risk of GDM (OR=1.17, 95% CI [0.94, 1.45], p=0.150) (Figure 3B).

Subgroup analysis

The differences in SI, SF, and Hb concentrations between the GDM and non-GDM groups were analyzed using subgroup analysis. For other iron metabolism indices, due to the low heterogeneity of or the small number of included literatures, subgroup analysis was not performed.

The subgroup analysis showed that in Asia, the Hb concentration was significantly higher in the GDM group than in the non-GDM group; however, there was no statistical difference for SI and SF. In the Middle East, the SI, SF, and Hb concentrations were significantly higher in the GDM group than in the non-GDM group; however, in Europe and America, the SF concentration was significantly higher in the GDM group than in the non-GDM group, while Hb concentration were not statistically different between the two groups (Table 3 and Table 4).

In the T1 stage of the pregnancy the SI and SF concentrations were significantly higher in the GDM group than in the non-GDM group; however, there was no statistical difference in the Hb concentration. In the T2 stage of the pregnancy the SI, SF, and Hb concentrations were significantly higher in the GDM group than in the non-GDM group. In the T3 stage of pregnancy the SF concentration was significantly higher in the GDM group than in the non-GDM group, while the SI and Hb concentrations were not statistically different between the two groups (Table 3 and Table 4).

In the case-control studies, the SI, SF, and Hb concentrations were significantly higher in the GDM group than in the non-GDM group. In the cohort studies, the SF concentration was significantly higher in the GDM group than in the non-GDM group, while the SI and Hb concentration were not different between the two groups (Table 3 and Table 4).

In large total population studies (sample size ≥150), the SI, SF, and Hb concentrations were significantly higher in the GDM group than in the non-GDM group. In small total population studies (sample size <150), the SF and Hb concentrations were significantly higher in the GDM group than in the non-GDM group, while there was no difference in the SI concentration between the two groups (Table 3 and Table 4).

For pregnant women aged ≥30 years, the SF and Hb concentrations were higher in the GDM group than in the non-GDM group and there was no difference of SI concentration between the two groups. For pregnant women aged <30 years, the SI and Hb concentrations were higher in the GDM group than in the non-GDM group and there was no difference of SF concentration between the two groups (Table 3 and Table 4).

DISCUSSION

In this study, SI concentration was significantly higher in

Table 3. Subgroup analysis of SI level difference between GDM and non-GDM groups

Grouping Method	Number of studies	SMD (95% CI)	I^2 (%)	$p^{\dagger}$	$p^{\ddagger}$
Overall	12	0.40 (0.16, 0.64)	81.3	<0.0001	<0.0001
Countries or regions					
Asia	3	0.44 (-0.24, 1.11)	94.9	<0.0001	0.208
Middle East	9	0.39 (0.11, 0.68)	81.3	<0.0001	0.006
Pregnancy stage					
T1	1	0.28 (0.15, 0.41)	-	-	<0.0001
T2	8	0.49 (0.12, 0.86)	92.1	<0.0001	0.010
T3	2	0.22 (-0.59, 1.03)	51.7	0.150	0.594
NR	1	0.19 (-0.17, 0.54)	-	-	0.307
Determination method					
Spectrophotometry	5	0.22 (-0.04, 0.49)	61.3	0.035	0.092
Automatic analyzer	3	0.24 (0.02, 0.45)	0	0.419	0.030
ICP-AES	2	0.02 (-0.08, 0.12)	0	0.331	0.753
Others	2	1.51 (0.75, 2.27)	80.4	0.024	0.000
Study type					
Case-control	10	0.47 (0.13, 0.82)	85.3	<0.0001	0.007
Cohort study	2	0.14 (-0.14, 0.41)	90.6	<0.0001	0.323
Total sample sizes					
≥150	5	0.37 (0.08, 0.66)	91.9	<0.0001	0.012
<150	7	0.43 (-0.09, 0.94)	84.7	<0.0001	0.103
Age of pregnant women					
≥30	3	-0.03 (-0.58, 0.51)	58.5	<0.0001	0.908
<30	7	0.39 (0.09, 0.70)	87.8	<0.0001	0.012
NR	2	1.08 (-0.54, 2.70)	96.6	<0.0001	0.190

NR: not reported in the study; Others: other methods of determination; SI: serum iron; GDM: gestational diabetes mellitus; T1: GDM before 12 weeks of gestation; T2: GDM between 13 and 28 weeks of gestation; T3: GDM after19 weeks of gestation; ICP-AES: Inductively Coupled Plasma-Atomic Emission Spectrometry

†The p value of heterogeneity test

‡The p value of significance.

patients with GDM than in those without GDM. Similar to our findings, Khambalia et al reported that the SI concentration of women with GDM was higher than in those without GDM.[40] In addition, Derbent et al[13] found that the SI concentration of IGT pregnant women with GDM was higher than in the healthy pregnant women; however, there was no correlation between SI concentration, fasting blood glucose, and 2 h postprandial blood glucose levels. An appropriate amount of iron is essential for cells, but a small amount of free iron, composed of redox iron (Fe^{2+}), can form reactive oxygen species (ROS), such as superoxide radicals and hydroxyl/lipid hydrogen peroxide radicals. Once produced, hydroxyl radicals damage DNA, proteins, and lipids through DNA oxidation, amino acid oxidation and lipid peroxidation, which can trigger senescence or cell death. Increased oxidative stress caused by iron excess may lead to pancreatic β cell damage, decreased insulin secretion, and impaired glucose regulation, leading to the occurrence of GDM.[41] Iron may also cause insulin resistance by reducing the liver's sensitivity to insulin, leading to reduced glucose uptake by fat cells and muscles. The enhanced oxidation of free fatty acids may lead to iron deposition in pancreatic beta cells, resulting in impaired insulin secretion.[7] Adiponectin enhances insulin signal transduction and inhibits gluconeogenesis, upregulates insulin gene expression and stimulates insulin secretion by activating peroxisome proliferator activated receptor in the liver, while iron overload leads to increased secretion of tumor necrosis factor-alpha (TNF-α), IL-6, IL-1β, and other inflammatory factors in macrophages, and inhibits adiponectin expression.[42] Iron overload produces ROS through the liver kinase -B1/mitogen-activated protein kinase signaling pathway, which inhibits insulin receptor phosphorylation in the liver, adipose tissue, muscle, and other organs, and reduces insulin receptor sensitivity.[43]

Consistent with previous results,[44] the present meta-analysis showed that SF concentration were higher in GDM patients than in those without GDM. In addition, compared with low SF levels, high SF levels were significantly associated with the risk of GDM, and the correlation between high SF level and the risk of GDM still existed after parameter adjustment. Sun et al[45] recently reported that the risk of GDM increased by 8% for every 10 μg/dL increase in SF concentration. Sharifi et al[34] found that high SF levels were significantly correlated with the risk of GDM, and the association remained after controlling confounding factors such as age, body mass index (BMI), family history of diabetes, systolic blood pressure, diastolic blood pressure, and previous history of GDM. However, the specific threshold at which elevated SF concentration are associated with GDM remains unclear. SF is a marker used to assess iron reserves throughout the body and is also an acute phase reactant. When the body is affected by inflammation, tumor, infection and other factors, SF levels increase. Women with both high C-reactive Protein (CRP) and high SF are at increased risk of GDM, suggesting that the systemic inflammation may be involved in GDM.[46] The levels of TNF-α, CRP, IL-6, IL-10, and other inflammatory markers in GDM patients were increased, interfered with insulin signaling, disrupted beta cell function, and imbalance in the expression of pro-inflammatory, and anti-inflammatory markers may directly lead to impaired glucose homeostasis.[47] The in-

Table 4. Subgroup analysis of SF and Hb level difference between GDM and non-GDM groups

Grouping Method	Number of studies	SMD (95%CI)	I^2 (%)	$p^{\dagger}$	$p^{\ddagger}$
SF					
Overall	15	0.58 (0.36, 0.81)	89.6	<0.0001	<0.0001
Countries or Regions					
Asia	2	1.00 (-0.07, 2.07)	96	<0.0001	0.067
Middle East	10	0.60 (0.29, 0.90)	89.5	<0.0001	<0.0001
Europe and USA	3	0.21 (0.09, 0.34)	0	0.514	0.001
Pregnancy Stage					
T1	4	0.20 (0.11, 0.28)	0	0.716	<0.0001
T2	9	0.81 (0.42, 1.21)	90.5	<0.0001	<0.0001
T3	2	0.33 (0.14, 0.53)	89.6	<0.0001	0.001
Study Type					
Case-control	14	0.60 (0.36, 0.85)	90.3	<0.0001	0.000
Cohort study	1	0.31 (0.08, 0.54)	-	-	0.009
Total Sample Sizes					
≥150	7	0.48 (0.24, 0.72)	89.6	<0.0001	<0.0001
<150	8	0.68 (0.19, 1.16)	88.8	<0.0001	0.006
Age of Pregnant Women					
≥30	6	0.69 (0.28, 1.11)	92.8	<0.0001	0.001
<30	7	0.50 (0.12, 0.87)	86.9	<0.0001	0.188
NR	2	0.58 (-0.28, 1.44)	90.8	0.001	0.009
Hb					
Overall	16	0.48 (0.28, 0.67)	94.4	<0.0001	<0.0001
Countries or Regions					
Asia	7	0.29 (0.11, 0.48)	91.3	<0.0001	0.001
Middle East	8	0.98 (0.38, 1.59)	96.4	<0.0001	0.001
Europe and USA	1	0.38 (-0.21, 0.97)	-	-	0.209
Pregnancy Stage					
T1	3	0.15 (-0.03, 0.33)	78.2	0.010	0.095
T2	9	1.05 (0.49, 1.60)	96.8	<0.0001	<0.0001
T3	3	0.11 (-0.14, 0.36)	54.1	0.113	0.386
Combined	1	0.00 (-0.15, 0.15)	-	-	1.000
Study Type					
Case-control	10	0.84 (0.44, 1.23)	95.8	<0.0001	<0.0001
Cohort study	6	0.17 (-0.02, 0.37)	84.2	<0.0001	0.076
Total Sample Sizes					
≥150	10	0.23 (0.09, 0.37)	89.1	<0.0001	0.002
<150	6	1.48 (0.28, 2.67)	96.9	<0.0001	0.015
Age of Pregnant Women					
≥30	5	1.39 (0.41, 2.36)	97.5	<0.0001	0.005
<30	9	0.28 (0.10, 0.46)	89.4	<0.0001	0.002
NR	2	0.62 (-0.64, 1.88)	95.4	<0.0001	0.337

NR: not reported in the study; SF: serum ferritin; Hb: hemoglobin; GDM: gestational diabetes mellitus.
†The p value of heterogeneity test.
‡The p value of significance.

creased SF levels in the GDM group were positively correlated with the homeostasis model assessment of insulin resistance (HOMA-IR). This suggests that ferritin may be involved in the process of insulin resistance, which is involved in regulating the transcription of SF and increasing the utilization of iron in peripheral tissues. However, when iron reserves in the body are excessive, iron-catalyzed hydroxyl radicals increase, causing oxidative stress and insulin resistance.[48]

In the present study, when age, BMI, parity, smoking, alcohol consumption, gestational stage at blood collection, and other factors were not adjusted, the concentration of Hb was positively correlated with the risk of GDM. However, when the above parameters were adjusted, the correlation disappeared, suggesting that the relationship between Hb and GDM may be affected by the above factors. A prospective observational study found that the prevalence of GDM was significantly increased in pregnant women with Hb levels in the highest quartile (>13 g/dL) at 24-28 weeks of gestation (18.7% vs 10.9%).[24] Gao et al[49] reported that a high Hb level (Hb ≥13 g/dL) was an independent risk factor for GDM, and the serum Hb concentration at stage T1 was positively correlated with BMI, postprandial blood glucose, and HOMA-IR. Taken together, elevated Hb levels may increase obesity, insulin resistance, and blood sugar levels.

In addition, TSAT levels in the GDM group were higher than that in the non-GDM group; however, there was no difference in the sTfR concentration between the two groups. In healthy individuals, TSAT is usually between 20% and 45%, reflecting the sufficient SI level required for erythropoiesis. Increased SI levels indicate iron overload, and increased maternal iron storage can affect glucose tolerance during pregnancy.[48] Bower et al[31] reported that with an increase in serum sTfR concentration, the risk of GDM gradually increased, but the association disappeared immediately after adjustment for age, exercise

during pregnancy, birth time, pre-pregnancy BMI, and low-density lipoprotein cholesterol.

Finally, in this study, serum TIBC concentration were lower in the GDM group than in the non-GDM group, while the serum hepcidin concentration was higher in the GDM group than in the non-GDM group. TIBC reflects the ability of Tf to combine with iron. In case of iron overload in the body, the free Tf content in the blood decreases, resulting in a lower TIBC level. Hepcidin is a central regulator of iron homeostasis, and excess iron increases the secretion of hepcidin through the binding of iron-Tf with TfR1 and TfR2 in the liver membrane.[50] Hepcidin controls the plasma iron levels by regulating the intestinal absorption of dietary iron, the release of hemoglobin iron in macrophage circulation, and the movement of stored iron in liver cells, which increases iron chelation in macrophages and liver to alleviate iron overload.[51] Decreased hepcidin expression increases iron absorption by upregulating the expression of TfR1 and DMT1, leading to intracellular iron accumulation and inducing increased iron deposition in β cells,[52] which affects insulin secretion.

In summary, serum iron, ferritin, transferrin saturation, hepcidin,and hemoglobin levels were higher and total iron binding ability was lower in GDM patients, and high serum ferritin and hemoglobin levels were associated with GDM risk. Therefore, on the one hand, women should regularly monitor the changes of serum iron metabolism during pregnancy. On the other hand, it is worth considering whether healthy women need routine preventive or selective iron supplementation during pregnancy. A study found that if pregnant women without iron deficiency anemia are given iron supplementation at T1 stage, the use of iron supplements is positively correlated with the increase of hemoglobin level and postpranpranal blood glucose level, and the risk of GDM also increases.[30] Routine iron supplementation may not be suitable for all pregnant women. How to formulate individualized iron supplementation regimen and select sensitive and accurate monitoring indicators are crucial for iron supplementation in pregnant women.

Conclusion

Serum iron, hemoglobin, ferritin, transferrin saturation, and hepcidin levels were higher and total iron binding ability was lower in patients with GDM than in those without GDM. High serum ferritin and hemoglobin levels were found to be associated with the risk of GDM; therefore, women should pay attention to serum levels of iron metabolism indices during pregnancy to prevent the occurrence of GDM.

AUTHOR DISCLOSURES

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