ORIGINAL RESEARCH

Association Between Serum Ferritin Concentration and Risk of Adverse Maternal and Fetal Pregnancy Outcomes: A Retrospective Cohort Study

Lanyao Yang[1,2,*], Lanlan Wu[3,*], Yao Liu[3], Hengying Chen[4], Yuanhuan Wei[3], Ruifang Sun[3], Siwen Shen[3], Bowen Zhan[1,2], Jianjun Yang[1,2], Guifang Deng[3]

[1]Department of Nutrition and Food Hygiene, School of Public Health and Management, Ningxia Medical University, Yinchuan, People's Republic of China; [2]Key Laboratory of Environmental Factors and Chronic Disease Control, School of Public Health and Management, Ningxia Medical University, Yinchuan, People's Republic of China; [3]Department of Clinical Nutrition, Union Shenzhen Hospital of Huazhong University of Science and Technology, Shenzhen, People's Republic of China; [4]Department of Maternal and Child Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China

*These authors contributed equally to this work

Correspondence: Guifang Deng, Department of Clinical Nutrition, Union Shenzhen Hospital of Huazhong University of Science and Technology, No. 89 Taoyuan Road, Shenzhen, Guangdong, 518052, People's Republic of China, Email misyfly@163.com; Jianjun Yang, Department of Nutrition and Food Hygiene, School of Public Health and Management, Ningxia Medical University, No. 1160 Shengli Road, Yinchuan, Ningxia, 750004, People's Republic of China, Email yangjj@nxmu.edu.cn

Objective: This study evaluated the associations of serum ferritin (SF) concentration during pregnancy with the risk of adverse maternal and fetal pregnancy outcomes.

Methods: We conducted a retrospective study of 2327 pregnant women from 2015 to 2020 in Guangdong, China. SF concentrations were measured at 16–18th and 28–32th week of gestation. Logistic regression models were applied to estimate the association between SF concentration and the risk of adverse pregnancy outcomes.

Results: After multivariable adjustment, the odds ratio (OR) of the highest quartile of SF concentration at 16–18th week of gestation was 1.43 (95% confidence interval [CI]: 1.09, 1.89) for gestational diabetes mellitus (GDM) and 1.79 (95% CI: 1.15, 2.79) for small for gestational age (SGA) when compared with the lowest quartile. At 28–32th week of gestation compared with the lowest quartile, women with SF in the highest quartile had an increased risk of SGA (OR: 1.62; 95% CI: 1.01, 2.62). Moreover, the lowest quartile of SF concentration decreased risk of SGA by 90% (95% CI: 0.01, 0.80) when compared with the highest quartile among pregnancy women with GDM.

Conclusion: Elevated SF concentrations increased the risk of GDM and SGA during pregnancy. Maintaining an appropriately low level of maternal SF at 28–32th week of gestation in women with GDM could reduce the risk of SGA.

Keywords: ferritin, adverse pregnancy outcomes, gestational diabetes mellitus, small for gestational age

Introduction

Nutritional needs are increased to supply the growing fetus and placenta, thus, nutrient such as iron deficiencies can easily occur during pregnancy.[1] Iron is a trace element essential for physiological functions, which is stored in the body as ferritin.[2,3] Maternal iron deficiency anaemia (IDA), usually accompanied by a drop in ferritin, unsurprisingly, is therefore prevalent among pregnant women across the globe, affecting about 42% of them.[4,5] IDA is widely recognized worldwide as a factor associated with adverse maternal and fetal outcomes. IDA may restrict the body's oxygen circulation, leading to oxidative stress or chronic hypoxia,[3,6] which is related to higher risk of low birth weight (LBW), preterm delivery and neonatal IDA,[7] which in turn can have long-lasting effects on intelligence, motor and behavioral development, and increase risk of IDA in future generations.[8]

However, it is worth noting that iron is a double-edged sword in the body system, with both iron deficiency and iron excess causing varying degrees of damage to health.[9] In addition to synthesizing hemoglobin and mediating cell growth

and development, iron is also a redox-active transitional metal with strong oxidation properties.[3] Therefore, it is crucial to assess the iron status of the body during pregnancy. Among them, serum ferritin (SF) is the most used clinically. Previous animal and epidemiological studies observed a significant association between excess SF storage and glucose metabolism disorders,[10–12] and others have found a positive association between ferritin and type 2 diabetes.[13,14] Then, some epidemiological studies have investigated the relationship between high SF concentrations and the incidence of gestational diabetes mellitus (GDM), but the results have been controversial. A case–control study from Western Asia showed that high SF levels were associated with an increased incidence of GDM,[15] as confirmed in a prospective observational study by Cheng et al of 851 Chinese subjects.[16] However, a prospective observational study from Lebanon did not find any significant association between a high SF concentration and the incidence of GDM in early pregnancy.[17] Furthermore, the relation between SF and adverse maternal and fetal pregnancy outcomes had also attracted attention. Recent studies indicated that SF concentrations were negatively correlated with birth weight in the third trimester, but this relationship is not significant in the second trimester.[1,18] Rahman et al only observed that elevated SF at gestational week 30 were positively associated with low birth weight (LBW).[18] Thus far, research on the association between high SF concentrations and more comprehensive adverse maternal and fetal pregnancy outcomes has been relatively limited. Besides, few studies have investigated differences in the effects of SF on pregnant women with and without GDM.

SF concentration change dramatically with the progresses of pregnancy because of physiological changes in maternal blood volume and increased iron requirements for the placenta and fetus.[9] In contrast to the measurement of SF concentrations from blood samples collected at single time points in previous studies, we collected blood samples at different time points to reliably analyze the relationship between high SF concentrations and the risk of adverse maternal and fetal pregnancy outcomes. Thus, we aimed to evaluate the relation between SF with the risk of development of GDM, and explore the association between SF concentrations and the risk of adverse pregnancy outcomes by detecting the SF concentration in different gestation stage in Chinese women.

Materials and Methods
Study Population
We conducted a retrospective study of 2419 pregnant women who had scheduled prenatal visits and planned to deliver their babies at the Union Shenzhen Hospital of the Huazhong University of Science and Technology from January 2015 to November 2020. All clinical data from the first antenatal examination to delivery were obtained from the hospital record information system and analyzed anonymously. Based on the following inclusion criteria, we established a cohort of pregnant women: 1) women aged ≥18 years; 2) singleton pregnancy; and 3) availability of complete medical records (including prenatal examination and delivery records). Participants with any of the following exclusion criteria were excluded: 1) twin and multiple pregnancy (n = 11); 2) pre-conceptional diabetes (n = 15); 3) hepatitis, or impaired liver function (n = 48); 4) nephritis or impaired kidney function (n = 5); 5) cardiovascular diseases (n = 3); and 6) acute respiratory infections (n = 10). Ultimately, after 92 pregnant women were excluded, 2327 pregnant women were included. Participants wrote informed consent forms at the beginning of the study. The protocol for this study was approved by the Ethics Committee of the Union Shenzhen Hospital of Huazhong University of Science and Technology (No. 2019072644) and carried out in accordance with the Declaration of Helsinki developed by the World Medical Association.

Laboratory Measurements
Venous blood samples were collected from the pregnant women at 16–18th and 28–32th weeks of gestation, and various biochemical indexes were measured. SF and hemoglobin concentrations were analyzed by a 7600–010 automatic analyzer (Hitachi, Tokyo, Japan) and hematology analyzer (Sysmex XN90000, Japan), respectively. The mean SF concentrations were derived from the average values measured at 16–18th and 28–32th weeks of gestation. The changes of SF concentrations were determined by subtracting the SF measured at 16–18th weeks of gestation from that measured at 28–32th weeks of gestation. The trajectory of SF concentrations was determined by the median concentration of SF at 16–18th and 28–32th weeks of gestation as the standard.

Maternal and Fetal Characteristics

Information on the maternal age, weight, height, educational background, pregnancy smoking and alcohol consumption status, history of diseases, history of gestation, and conception method were collected using questionnaires and by reviewing records in the hospital information system. Maternal body mass index (BMI) (kg/m2) was calculated as weight (kg) divided by height squared (m2). Parity was interpreted as the number of live or stillborn infants before this pregnancy. The gestational age at delivery (weeks) was determined by the time of the last menstrual period until the time of delivery.

Information on the gender and physical characteristics of the newborns was obtained by reviewing records in the hospital information system. Neonatal weight, height, head circumferences and chest circumferences were measured at the time of birth using infant length and weight measuring instrument and soft ruler, respectively.

Definitions of the Adverse Maternal and Fetal Pregnancy Outcomes

We designated GDM, premature birth, macrosomia, LBM, large for gestational age (LGA), and SGA as adverse maternal and fetal pregnancy outcomes. The 75-g oral glucose tolerance test was conducted as recommended by the International Association of Diabetes and Pregnancy Research Groups (IADPSG).[19] At 24–28th week of gestation, maternal blood samples were collected at 0, 1, and 2 h after the administration of 75 g of glucose (loading dose) to determine the serum glucose concentration. Based on the IADPSG criteria, GDM was diagnosed when one of the following criteria were met: fasting plasma glucose ≥5.1 mmol/L; 1-h plasma glucose ≥10.0 mmol/L; or 2-h plasma glucose ≥8.5 mmol/L. Premature birth was defined as the birth of a newborn whose gestational age was <37 weeks. Following the latest standards in China, newborns with a weight of >4000 g were determined as macrosomia, those with a weight of <2500 g were designated as LBW, and those with a birth weight below the 10th percentile or above the 90th percentile of the average weight of other newborns of the same gestational age were defined as being SGA and LGA, respectively.[20] Similarly, according to the 10th or 90th percentile of the same age newborns, we define short state at birth, tall stature at birth, small head circumference and big head circumference, respectively.[20]

Statistical Analyses

Participants were divided into four groups based on the SF concentration quartiles. Continuous variables were expressed as the median (quartiles) and categorical variables as percentages (%). Differences between groups were assessed using Kruskal–Wallis test for continuous variables, or chi-square test for categorical variables. Using the lowest groups as the reference group for all subjects, logistic regression analysis was performed to assess the ORs and 95% CIs for the risk of adverse maternal and fetal pregnancy outcomes. Baseline variables that were considered clinically relevant or that showed a univariate relationship with outcome were entered into multivariable adjusted models. Finally, the multivariable-adjusted model was adjusted for age, BMI, education background, smoking status, alcohol consumption status, parity, abortion history, conception method, thalassemia history and hemoglobin concentrations. Furthermore, pregnant women with or without GDM were divided into two subgroups, logistic regression analysis was performed using the fourth SF concentration quartile as the reference group. The association of the changes and the mean SF concentrations with pregnancy outcomes were also analyzed. SPSS version 21.0 (SPSS Inc., Chicago, IL, USA) was used to analyze our data. A two-sided P value <0.05 was considered as statistically significant.

Results

Participant Characteristics

We conducted a retrospective study of 2327 Chinese pregnant women. As presented in Table 1, significant differences in terms of the maternal alcohol consumption status, hemoglobin concentrations, the 1-h and 2-h post-load glucose concentrations, and SF at 16–18th and 28–32th week of gestation were detected between the four quartiles (all P < 0.05). We found that the prevalence of GDM and SGA (P = 0.026 and P = 0.029, respectively) was significantly elevated in the higher quartiles of SF concentration. No significant difference was discovered in other indicators.

Association Between SF Concentration and the Risk of GDM

In Table 2, we found that the SF concentration at 16–18th weeks of gestation increased and the incidence of GDM changed, with values of 20.5%, 22.4%, 21.4% and 27.4%. After adjusting for the covariates, the highest SF concentration

Table 1 Baseline Characteristics of Participants According to Quartiles of SF at 16–18th Weeks of Gestation

Characteristic	Total	SF at 16–18th Weeks of Gestation (ug/L)				P value
		Quartile 1 <18.32	Quartile 2 18.32–31.34	Quartile 3 31.34–55.90	Quartile 4 >55.90	
Number of cases	2327	584	580	583	580	
Maternal characteristic						
Maternal age (years)	31.0 (29.0, 35.0)	31.0 (29.0, 34.0)	32.0 (29.0, 35.0)	32.0 (29.0, 34.0)	31.0 (29.0, 35.0)	0.365
BMI (kg/m²)	20.5 (18.8, 22.3)	20.4 (18.8, 22.1)	20.4 (18.8, 22.2)	20.6 (19.0, 22.3)	20.6 (18.8, 22.5)	0.634
BMI categories						0.527
< 24.0 (n, %)	2057 (88.4%)	526 (90.1%)	508 (87.6%)	514 (88.2%)	509 (87.8%)	
≥24.0 (n, %)	270 (11.6%)	58 (9.9%)	72 (12.4%)	69 (11.8%)	71 (12.2%)	
Education background						0.477
Primary (n, %)	5 (0.2%)	2 (0.3%)	1 (0.2%)	0 (0.0%)	2 (0.3%)	
Secondary (n, %)	488 (21.0%)	131 (22.5%)	130 (22.4%)	114 (19.6%)	113 (19.5%)	
College and above (n, %)	1834 (78.8%)	451 (77.2%)	449 (77.4%)	469 (80.4%)	465 (80.2%)	
Smoking status (n, %)	6 (0.3%)	1 (0.2%)	2 (0.3%)	0 (0.0%)	3 (0.5%)	0.237
Alcohol consumption status (n, %)	7 (0.3%)	5 (0.9%)	2 (0.3%)	0 (0.0%)	0 (0.0%)	0.018
Conception method (n, %)						0.939
Natural	2308 (99.2%)	578 (99.0%)	576 (99.3%)	579 (99.3%)	575 (99.1%)	
Artificial	19 (0.8%)	6 (1.0%)	4 (0.7%)	4 (0.7%)	5 (0.9%)	
Parity						0.469
Nulliparity (n, %)	1724 (74.1%)	441 (75.5%)	416 (71.7%)	437 (75.0%)	430 (74.1%)	
Multipara (n, %)	603 (25.9%)	143 (24.5%)	164 (28.3%)	146 (25.0%)	150 (25.9%)	
Abortion history (n, %)	745 (32.0%)	178 (30.5%)	192 (33.1%)	182 (31.2%)	193 (33.3%)	0.673
Thalassemia history (n, %)	127 (5.5%)	34 (5.8%)	35 (6.0%)	28 (4.8%)	30 (5.2%)	0.777
Gestational age at delivery (weeks)	39.0 (38.0, 40.0)	39.0 (38.0, 40.0)	39.0 (38.0, 40.0)	39.0 (38.0, 40.0)	39.0 (38.0, 40.0)	0.873
SF at 16–18th weeks of gestation (μg/L)	31.3 (18.3, 55.9)	12.2 (9.3, 14.7)	24.2 (21.0, 27.8)	42.0 (36.3, 48.3)	82.6 (62.3, 113.1)	< 0.001
SF at 28–32th weeks of gestation (μg/L)	23.9 (16.0, 32.7)	21.7 (14.9, 31.0)	23.0 (14.7, 30.6)	24.6 (16.6, 33.5)	26.6 (18.6, 35.9)	< 0.001
Hemoglobin (g/L)	116.0 (111.0, 122.0)	114.2 (108.0, 120.0)	118.0 (111.5, 123.0)	117.0 (112.0, 123.0)	116.0 (111.0, 123.0)	< 0.001
Glucose metabolism						
Fasting blood glucose (mmol/l)	4.6 (4.4, 4.8)	4.5 (4.4, 4.7)	4.6 (4.4, 4.7)	4.5 (4.4, 4.8)	4.5 (4.3, 4.8)	0.798
1-h post-load glucose (mmol/l)	8.0 (7.0, 9.2)	8.0 (6.9, 9.1)	8.0 (7.0, 9.2)	7.8 (6.8, 9.0)	8.2 (7.0, 9.3)	0.028
2-h post-load glucose (mmol/l)	6.9 (6.1, 7.8)	6.9 (6.1, 7.8)	6.9 (6.1, 7.9)	6.8 (6.0, 7.7)	7.0 (6.2, 7.9)	0.027
Newborn characteristics						
Sex						0.171
Female (n, %)	1085 (46.6%)	252 (43.2%)	288 (49.7%)	274 (47.1%)	271 (46.7%)	
Male (n, %)	1241 (53.4%)	332 (56.8%)	292 (50.3%)	308 (52.9%)	309 (53.3%)	
Birth weight (g)	3300.0 (3000.0, 3550.0)	3300.0 (3035.0, 3600.0)	3250.0 (3007.5, 3550.0)	3250.0 (3000.0, 3550.0)	3250.0 (2955.0, 3500.0)	0.055
Birth length (cm)	50.0 (49.0, 51.0)	50.0 (49.0, 51.0)	50.0 (49.0, 51.0)	50.0 (49.0, 51.0)	50.0 (49.0, 51.0)	0.101
Head circumference (cm)	34.0 (33.0, 35.0)	34.0 (33.0, 35.0)	34.0 (33.0, 35.0)	34.0 (33.0, 35.0)	34.0 (33.0, 35.0)	0.114
Chest circumference (cm)	33.0 (32.0, 34.0)	33.0 (32.0, 34.8)	33.0 (32.0, 34.0)	33.0 (32.0, 34.0)	33.0 (32.0, 34.0)	0.516
Adverse maternal and fetal outcomes						
GDM (n, %)	534 (22.9%)	120 (20.5%)	130 (22.4%)	125 (21.4%)	159 (27.4%)	0.026
Premature birth (n, %)	116 (5.0%)	27 (4.6%)	29 (5.0%)	28 (4.8%)	32 (5.5%)	0.903
Macrosomia (n, %)	86 (3.7%)	25 (4.3%)	17 (2.9%)	23 (3.9%)	21 (3.6%)	0.659
LBW (n, %)	96 (4.1%)	23 (3.9%)	26 (4.5%)	22 (3.8%)	25 (4.3%)	0.926
LGA (n, %)	270 (11.6%)	72 (12.3%)	64 (11.0%)	73 (12.5%)	61 (10.5%)	0.654
SGA (n, %)	166 (7.1%)	35 (6.0%)	34 (5.9%)	40 (6.9%)	57 (9.8%)	0.029
Tall stature at birth	124 (5.3%)	32 (5.5%)	25 (4.3%)	34 (5.8%)	33 (5.7%)	0.646
Short stature at birth	96 (4.1%)	30 (5.1%)	18 (3.1%)	27 (4.6%)	21 (3.6%)	0.285
Big head circumference	317 (13.6%)	86 (14.7%)	66 (11.4%)	96 (16.5%)	69 (11.9%)	0.036
Small head circumference	93 (4.0%)	16 (2.7%)	16 (2.8%)	30 (5.1%)	31 (5.3%)	0.024

Notes: Data were expressed as the median (quartiles) for continuous variables and as n (%) for categorical variables. *P* values for continuous variables were determined by Kruskal–Wallis test and categorical variables were determined by chi-square test.
Abbreviations: SF, serum ferritin; BMI, body mass index; GDM, gestational diabetes mellitus; LBW, low birth weight; LGA, large for gestational age; SGA, small for gestational age.

Table 2 Odds Ratios (95% Confidence Intervals) for the Occurrence of GDM According to the SF at 16–18th Weeks of Gestation

	SF at 16–18th Weeks of Gestation (ug/L)				*P* Trend	Per-SD Increase
	Quartile 1 <18.32	Quartile 2 18.32–31.34	Quartile 3 31.34–55.90	Quartile 4 >55.90		
n (%)	120 (20.5%)	130 (22.4%)	125 (21.4%)	159 (27.4%)		
OR (95% CI)	1.00 (ref)	1.12 (0.84–1.48)	1.06 (0.80–1.40)	1.46 (1.11–1.92)	0.026	1.15 (1.05–1.26)
AOR (95% CI)						
Model 1	1.00 (ref)	1.06 (0.80–1.41)	1.02 (0.77–1.36)	1.45 (1.10–1.91)	0.022	1.16 (1.06–1.27)
Model 2	1.00 (ref)	1.05 (0.79–1.40)	1.01 (0.76–1.35)	1.43 (1.09–1.89)	0.025	1.16 (1.05–1.27)

Notes: Model 1 adjusted for age, BMI. Model 2 adjusted for the variables in Model 1 plus education background, smoking status, alcohol consumption status, conception method, parity, abortion history, thalassemia history and hemoglobin.
Abbreviations: SF, serum ferritin; GDM, gestational diabetes mellitus, OR odds ratio, AOR, adjusted odds ratio.

quartile was significantly associated with an increased risk of developing GDM (AOR: 1.43, 95% CI: 1.09, 1.89) when compared with the lowest quartile. Each SD increase in the SF concentration was associated with a 16% (AOR: 1.16, 95% CI: 1.05, 1.27) increase in the risk of developing GDM.

Association Between SF Concentration and the Risk of Adverse Pregnancy Outcomes

As shown in Tables 3 and 4, the AOR for SGA in the highest SF concentration quartile compared with the lowest quartile was 1.79 (95% CI: 1.15, 2.79) at 16–18th weeks of gestation and 1.62 (95% CI: 1.01, 2.62) at 28–32th weeks of

Table 3 Odds Ratios (95% Confidence Intervals) for the Occurrence of Adverse Maternal and Fetal Outcomes According to the SF at 16–18th Weeks of Gestation

Outcomes	SF at 16–18th Weeks of Gestation (ug/L)				*P* Trend	Per-SD Increase
	Quartile 1 <18.32	Quartile 2 18.32–31.34	Quartile 3 31.34–55.90	Quartile 4 >55.90		
N	584	580	583	580		
Premature birth						
Rate (%)	27 (4.6%)	29 (5.0%)	28 (4.8%)	32 (5.5%)	0.903	
OR (95% CI)	1.00 (ref)	1.09 (0.63–1.86)	1.04 (0.61–1.79)	1.21 (0.71–2.04)	0.908	1.04 (0.87–1.25)
AOR (95% CI)	1.00 (ref)	1.10 (0.64–1.89)	1.07 (0.62–1.85)	1.26 (0.74–2.14)	0.853	1.06 (0.89–1.27)
Macrosomia						
Rate (%)	25 (4.3%)	17 (2.9%)	23 (3.9%)	21 (3.6%)	0.659	
OR (95% CI)	1.00 (ref)	0.68 (0.37–1.26)	0.92 (0.52–1.64)	0.84 (0.47–1.52)	0.657	1.04 (0.85–1.28)
AOR (95% CI)	1.00 (ref)	0.67 (0.35–1.26)	0.91 (0.51–1.64)	0.84 (0.46–1.52)	0.643	1.04 (0.85–1.27)
LBW						
Rate (%)	23 (3.9%)	26 (4.5%)	22 (3.8%)	25 (4.3%)	0.926	
OR (95% CI)	1.00 (ref)	1.15 (0.65–2.03)	0.96 (0.53–1.74)	1.10 (0.62–1.96)	0.925	1.06 (0.88–1.29)
AOR (95% CI)	1.00 (ref)	1.21 (0.68–2.16)	1.02 (0.56–1.86)	1.17 (0.65–2.09)	0.892	1.08 (0.89–1.30)
LGA						
Rate (%)	72 (12.3%)	64 (11.0%)	73 (12.5%)	61 (10.5%)	0.654	
OR (95% CI)	1.00 (ref)	0.88 (0.62–1.26)	1.02 (0.72–1.44)	0.84 (0.58–1.20)	0.654	0.95 (0.83–1.09)
AOR (95% CI)	1.00 (ref)	0.84 (0.58–1.21)	0.99 (0.69–1.42)	0.81 (0.56–1.18)	0.557	0.94 (0.82–1.08)
SGA						
Rate (%)	35 (6.0%)	34 (5.9%)	40 (6.9%)	57 (9.8%)	0.029	
OR (95% CI)	1.00 (ref)	0.98 (0.60–1.59)	1.16 (0.72–1.85)	1.71 (1.10–2.65)	0.032	1.21 (1.07–1.38)
AOR (95% CI)	1.00 (ref)	1.06 (0.65–1.73)	1.22 (0.76–1.97)	1.79 (1.15–2.79)	0.032	1.21 (1.06–1.38)

Notes: Logistic regression models were adjusted for age, BMI, education background, smoking status, alcohol consumption status, conception method, parity, abortion history, thalassemia history and hemoglobin.
Abbreviations: SF, serum ferritin; LBW, low birth weight; LGA, large for gestational age; SGA, small for gestational age; OR odds ratio; AOR, adjusted odds ratio.

Table 4 Odds Ratios (95% Confidence Intervals) for the Occurrence of Adverse Maternal and Fetal Outcomes According to the SF at 28–32th Weeks of Gestation

Outcomes	SF at 28–32th Weeks of Gestation (ug/L)				P Trend	Per-SD Increase
	Quartile 1 <16.01	Quartile 2 16.01–23.91	Quartile 3 23.91–32.71	Quartile 4 >32.71		
N	582	582	582	581		
Premature birth						
Rate (%)	25 (4.3%)	31 (5.3%)	33 (5.7%)	27 (4.6%)	0.692	
OR (95% CI)	1.00 (ref)	1.25 (0.73–2.15)	1.34 (0.79–2.28)	1.09 (0.62–1.89)	0.697	1.02 (0.85–1.22)
AOR (95% CI)	1.00 (ref)	1.21 (0.70–2.09)	1.31 (0.77–2.25)	1.05 (0.60–1.85)	0.730	1.01 (0.84–1.22)
Macrosomia						
Rate (%)	27 (4.6%)	25 (4.3%)	22 (3.8%)	12 (2.1%)	0.090	
OR (95% CI)	1.00 (ref)	0.92 (0.53–1.61)	0.81 (0.45–1.44)	0.43 (0.22–0.86)	0.106	0.70 (0.53–0.94)
AOR (95% CI)	1.00 (ref)	0.87 (0.49–1.53)	0.76 (0.42–1.36)	0.42 (0.21–0.84)	0.096	0.69 (0.51–0.93)
LBW						
Rate (%)	17 (2.9%)	28 (4.8%)	28 (4.8%)	23 (4.0%)	0.319	
OR (95% CI)	1.00 (ref)	1.68 (0.91–3.10)	1.68 (0.91–3.10)	1.37 (0.72–2.59)	0.321	1.06 (0.88–1.28)
AOR (95% CI)	1.00 (ref)	1.71 (0.92–3.18)	1.75 (0.94–3.25)	1.41 (0.74–2.69)	0.282	1.06 (0.88–1.28)
LGA						
Rate (%)	70 (12.0%)	64 (11.0%)	70 (12.0%)	66 (11.4%)	0.933	
OR (95% CI)	1.00 (ref)	0.90 (0.63–1.30)	1.00 (0.70–1.42)	0.94 (0.66–1.34)	0.930	0.97 (0.85–1.10)
AOR (95% CI)	1.00 (ref)	0.86 (0.60–1.24)	0.96 (0.67–1.37)	0.92 (0.64–1.32)	0.873	0.96 (0.84–1.10)
SGA						
Rate (%)	32 (5.5%)	46 (7.9%)	41 (7.0%)	47 (8.1%)	0.298	
OR (95% CI)	1.00 (ref)	1.48 (0.93–2.35)	1.30 (0.81–2.10)	1.51 (0.95–2.41)	0.303	1.16 (1.02–1.33)
AOR (95% CI)	1.00 (ref)	1.54 (0.96–2.48)	1.39 (0.86–2.26)	1.62 (1.01–2.62)	0.208	1.17 (1.03–1.34)

Notes: Logistic regression models were adjusted for age, BMI, education background, smoking status, alcohol consumption status, conception method, parity, abortion history, thalassemia history and hemoglobin.
Abbreviations: SF, serum ferritin; LBW, low birth weight; LGA, large for gestational age; SGA, small for gestational age; OR odds ratio; AOR, adjusted odds ratio.

gestation. Each SD increase in the SF concentration at 16–18th weeks of gestation was associated with a 21% (AOR: 1.21, 95% CI: 1.06, 1.38) increase in the risk of SGA; the same increase at 28–32th weeks of gestation was associated with a 17% (AOR: 1.17, 95% CI: 1.03, 1.34) increase in the risk of SGA. In Supplementary Table 1, compared with the lowest quartile, the AOR of Small head circumference in the highest SF concentration quartile was 2.05 (95% Cl: 1.10, 3.80) and 1.97 (95% Cl: 1.05, 3.69) at 16–18 weeks of gestation and 28–32 weeks of gestation, respectively. We also found the same association between SF concentration and larger body length (AOR: 2.01, 95% CI: 1.15, 3.50) at 28–32 weeks of gestation. No significant difference was observed between SF concentration and other pregnancy outcomes.

Association Between SF Concentration at 28–32th Week of Gestation and the Risk of Adverse Pregnancy Outcomes Among Pregnancy Women with and without GDM

Figure 1 outlines that the lowest SF concentration quartile was significantly associated with a 90% decreased risk of SGA (AOR: 0.10, 95% CI: 0.01, 0.80) when compared with the highest quartile among pregnancy women with GDM. There was no significant difference between SF concentration and adverse pregnancy outcomes among pregnancy women without GDM.

The Association Between the Mean, Changes and Trajectory of SF Concentration and the Risk of Adverse Pregnancy Outcomes

In Supplementary Table 2, the highest quartile of mean SF concentration had a 78% (OR: 1.78, 95% CI: 1.15, 2.74) increased risk of SGA. The associations between the changes of SF concentration across the 16–18th and 28–32th week of gestation with adverse pregnancy outcomes are presented in Supplementary Table 3. The AOR for the risk of SGA in
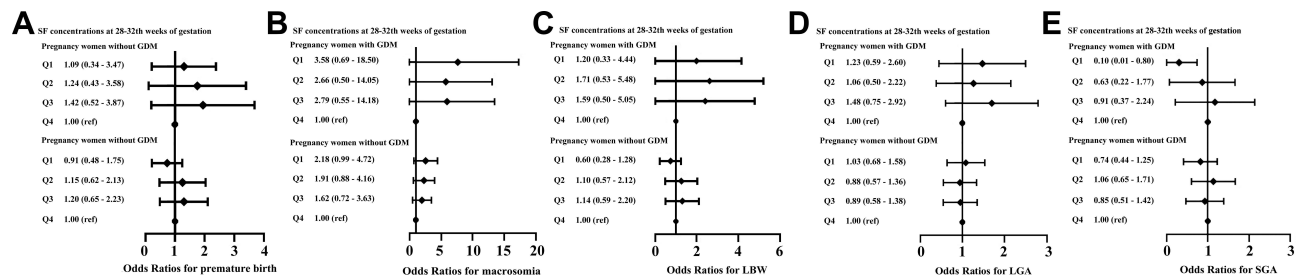
Figure 1 The association between SF and the risk of adverse pregnancy outcomes among pregnancy women with and without GDM. The model was adjusted for age, BMI, education background, smoking status, alcohol consumption status, conception method, parity, abortion history, thalassemia history and hemoglobin.

the highest quartile was 1.61 (95% CI: 1.04, 2.50) when compared with the lowest quartile. As shown in Supplementary Table 4, compared with the low-to-low-level, the high-to-high level was significantly associated with a 63% increase in SGA risk (AOR: 1.63, 95% CI: 1.06, 2.51).

Discussion

In this retrospective cohort study among Chinese pregnancy women, we observed an increased risk of GDM with elevated SF concentration at 16–18th week of gestation, and the elevated SF concentration at both 16–18th and 28–32th week of gestation was associated with the increased risk of SGA. It is worth mentioning that low SF concentration at 28–32th week of gestation had a decreased risk of SGA among pregnant women with GDM. Moreover, the study also found that more drastic changes in SF concentrations across the 16–18th and 28–32th week of gestation were attributed to a higher risk of developing SGA. The same effect was seen with higher mean SF concentration.

A series of studies have reported the relationship between SF concentration and insulin resistance (IR). SF is a major ferrous storage globulin with a complex structure and is an indicator of iron storage.[17,21] Excess iron can catalyze excessive reactive oxygen species (ROS) production.[3] ROS are produced by aerobic cells during normal metabolism and can induce cell apoptosis or damage tissues through the cellular oxidative stress response.[22,23] Under normal physiological conditions, the generation and elimination of ROS are dynamically balanced. As iron storage increases, the excess iron ions increase the amount of ROS produced.[24,25] Consequently, high amounts of iron can restrict the synthesis and secretion of insulin through oxidative stress, leading to the development of IR and the accelerated progression of GDM.[26] Second, excess iron is also involved in the development of IR by activating nuclear factor-κ B in macrophages and Kupffer cells, which in turn increases the release of tumor necrosis factor a and downregulates insulin signaling.[27,28] Consistent with most studies, our study discovered that elevated SF concentrations at the second trimester (16–18th week of gestation) were associated with an increased risk of the developing of GDM. Similar results were reported by a case–control study from Western Asia[15] and another prospective cohort study from China,[29] that is, high SF concentrations at 14–18th week of gestation were associated with an increased incidence of GDM (OR: 2.72, 95% CI: 1.76, 4.21). Although our study did not record SF concentrations in the first trimester, several studies that focused on the first trimester of pregnancy have reported results consistent with our findings. A prospective observational study of 851 people observed that elevated SF concentrations in the first trimester were associated with an increased risk of GDM (OR: 2.31, 95% CI: 1.30, 4.10).[16] However, a few studies have come to a different conclusion. Chan et al conducted a randomized controlled trial and found no significant difference in the risk of GDM between groups with high SF concentrations and corresponding control groups (OR: 1.04, 95% CI: 0.70, 1.53).[30] Another prospective observational study from Lebanon indicated that there were no significant associations between high SF and the incidence of GDM in early pregnancy.[17] However, the overall SF concentration recorded in their study was low and the cut-off value for the highest SF concentration quartile was only 38.5 g/L,[17] whereas the cut-off value for our study was 55.9 µg/L, which may be the reason for the different results.

Few studies have paid attention to the association between a high SF concentration and the risk of adverse pregnancy outcomes. A retrospective cohort study of 11,581 people from China reported that low SF concentrations were not only correlation with an increased risk of macrosomia (OR: 1.27, 95% CI: 1.07, 1.51), but also with a reduced risk of LBW (OR: 0.68, 95% CI: 0.49, 0.93) and SGA (OR: 0.74, 95% CI: 0.63, 0.86).[31] Shaji Geetha et al found that higher maternal

serum ferritin concentrations were associated with higher risk of preeclampsia.[32] No consistent associations were present of maternal ferritin in early pregnancy with the risks of gestational hypertensive disorders as reported in a population-based prospective cohort study among 5983 pregnant women.[33] Similar associations were found in our study, with elevated SF concentrations associated with an increased risk of SGA. However, we did not discover any significant associations between SF concentration and the risks of macrosomia, gestational hypertensive disorders and LBW. The reason for the discrepancy may be explained by the different ethnicities of the participants, variations in study design, time points of SF concentration measurement, diagnostic criteria, and other confounding factors.[18,31,34,35] In their study, iron deficiency (ferritin < 12 ug/L) accounted for 52% of the total population,[31] compared with only 12% in our cohort. Moreover, the time points of SF concentration measurement were also later than ours. Rahman's study showed that the elevated SF concentration at the 30th week of pregnancy was associated with the increased risk of LBW, while no such correlation was found at the 14th week of pregnancy.[18] The mechanism underlying the adverse effect of high SF concentrations on maternal and perinatal outcomes remains unclear. The possible mechanisms are as follows: First, higher maternal ferritin may affect fetal development through oxidative stress, lipid peroxidation, and DNA damage in placental cells.[36] Then, notably, iron build-up may also increase blood viscosity and reduce uteroplacental blood flow, thereby impairing fetal development.[37]

One striking finding from this study was the risk of SGA reduced with the appropriate decrease of SF concentrations at 28–32th week of gestation among pregnancy women with GDM. In China, GDM is routinely diagnosed at 24–28 weeks of gestation by the 75-g oral glucose tolerance test. We can predict and intervene it by measuring SF concentration as early as possible, and get a better prognosis. Another interesting finding from our study was that more drastic increases in SF concentrations from the 16–18th to 28–32th week of gestation were associated with a higher risk of developing SGA. Compared with the low-to-low-level of the trajectory SF concentrations, the high-to-high level had higher risk of SGA. In addition, the risk of SGA increased with the mean SF concentration at 16–18th and 28–32th week of gestation. These results further emphasize the importance of monitoring SF concentrations throughout pregnancy. In China, routine iron supplementation is generally recommended from the third month of pregnancy and regular blood tests are performed at each trimester of pregnancy.[38] Our studies may suggest maintaining a slightly lower value rather than a larger value within the normal range of serum ferritin, shortening follow-up intervals and increasing the number of follow-up, providing personalized guidance for pregnant women with respect to iron supplementation based on SF concentration at different stages of pregnancy to mitigate the risk of adverse maternal and fetal pregnancy outcomes.

There are several limitations to this study. First, all of the subjects included were from China. This relatively limited population source might have led to selection bias. Second, although the major risk factors were recognized and adjusted for in the model, some unmeasured or unknown residual confounders remained. For instance, we lacked information on inflammatory markers, which may have affected our results as acute or chronic inflammation can affect SF concentrations.[39,40] We excluded women with known inflammatory diseases to minimize this effect.

Conclusion

Elevated SF concentrations at 16–18th week of gestation were associated with increased risks of GDM and SGA. At 28–32th week of gestation, women with higher SF concentrations faced an increased risk of SGA. Furthermore, the risk of SGA reduced with the appropriate decrease of SF concentrations at 28–32th week of gestation among pregnancy women with GDM. Therefore, SF concentration is a good indicator of the risk of adverse maternal and fetal pregnancy outcomes and can help provide personalized guidance for pregnant women with respect to iron supplementation at different stages of pregnancy.

Highlights

1. The risk of SGA reduced with the appropriate decrease of SF concentrations at 28–32th weeks of gestation among pregnancy women with GDM;
2. More drastic changes in SF concentrations across the 16–18th and 28–32th weeks of gestation were attributed to a higher risk of developing SGA;
3. Higher mean SF concentration contributes to developing SGA;
4. The association between SF and adverse maternal and fetal pregnancy outcomes was studied in a relatively large sample.

Abbreviations

SF, Serum ferritin; GDM, Gestational diabetes mellitus; OR, Odds ratio; AOR, Adjusted odds ratio; CI, Confidence interval; SGA, Small for gestational age; IDA, Iron deficiency anaemia; BMI, Body mass index; LBW, Low birth weight; LGA, large for gestational age; ROS, Reactive oxygen species; IR, insulin resistance.

Data Sharing Statement

To protect the privacy of pregnant women, the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Participants written informed consent forms at the beginning of the study. The protocol for this study was approved by the Ethics Committee of the Union Shenzhen Hospital of Huazhong University of Science and Technology (No. 2019072644) and all methods were performed in accordance with the relevant guidelines and regulations (Declaration of Helsinki).

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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