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Maternal iron nutrition during pregnancy and fetal intrauterine growth

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Abstract

Background Iron is critical for maternal and fetal health; however, the effect of iron nutrition on fetal intrauterine growth remains unclear. This study aimed to investigate the associations of maternal iron nutrition during pregnancy with fetal intrauterine growth parameters among the Chinese population.

Methods This retrospective birth cohort study included 482 pregnant women. Maternal information was collected by standard questionnaires. Maternal concentrations of serum ferritin and hemoglobin were detected. Fetal ultrasound examinations in the second and third trimesters were conducted. Quantile regression or linear regression models were applied to assess the associations.

Results Participants took iron supplementation in early, mid, and late pregnancy accounted for 19.1%, 40.3%, and 37.8%, respectively. Iron supplementation in the first and second trimesters and total iron intake in pregnancy were positively associated with fetal intrauterine growth parameters at some percentiles. Compared with those without iron supplementation in the second trimester, women with iron supplementation in the second trimester had 0.37 (95%CI = 0.24–0.49), 0.37 (95%CI = 0.26–0.48), 0.15 (95%CI = 0.04–0.26), and 0.52 (95%CI = 0.42–0.61) higher z-scores in fetal biparietal diameter, femur length, abdominal circumference, and estimated fetal weight at the 50th percentile in the second trimester, respectively. Maternal serum ferritin and hemoglobin concentrations in the first and second trimesters were positively correlated with several fetal growth parameters.

Conclusions Fetal intrauterine growth may benefit from maternal iron nutrition in the first and second trimesters.

Keyword Iron intake, Iron status, Pregnancy, Fetal growth

Introduction

Normal fetal intrauterine growth is a key component of healthy pregnancy and has an important impact on health throughout the life cycle [1, 2]. Abnormal fetal growth, especially fetal growth restriction, can lead to permanent changes in the structure and function of the body, and increase the risk of perinatal mortality and morbidity as well as chronic non-communicable diseases [3, 4]. Recent evidence has showed that fetal intrauterine growth is associated with perinatal outcomes, childhood growth and development, and adult metabolic health [5, 6]. Therefore, it is important to identify modifiable risk factors to implement preventive strategies to improve fetal intrauterine growth.

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Maternal nutrition during pregnancy, as a key modifiable factor, is critical for fetal growth [7–9]. Iron deficiency is the most common nutritional deficiency among pregnant women worldwide because of the expansion of red cell mass and the growth of fetal-placental unit in pregnancy [10]. Maternal iron deficiency is reported to have adverse effects on pregnancy outcomes, such as miscarriage, premature delivery, low birth weight, and birth defects [11–14]. Dietary and supplemental iron are important sources of iron for pregnant women [13]. Pregnant women have different requirements for iron during different trimesters, and the increase in iron demand is mainly in the second and third trimesters. To meet the increased iron requirements, pregnant women are typically recommended to take iron supplementation in pregnancy in some countries including the USA, the UK, and Canada [15]. However, iron supplements provision in pregnancy is not part of standard practice of care in most countries including China [13]. Maternal iron intake from diets and supplements could influence iron status in the body, and further exert effects on maternal and fetal health [16].

Prior studies have showed the association between iron nutrition during pregnancy and fetal growth by using physical measurement data at birth mainly birth weight [13, 17–20]. However, there are few human studies focusing on iron nutrition and fetal intrauterine growth [21–23]. Fetal intrauterine growth is a dynamic and continuous process; thus only monitoring the physical indicators at birth cannot detect and intervene early abnormalities of fetal growth [24]. Fetal ultrasound examinations during pregnancy can monitor fetal intrauterine growth in real time through the parameters such as biparietal diameter (BPD), femur length (FL), abdominal circumference (AC), and estimated fetal weight (EFW), and help characterize fetal growth in advance compared with the birth measurements [24]. However, to our knowledge, there has been no human study to comprehensively explore the associations of maternal iron nutrition integrating iron supplementation, dietary iron, and iron status with fetal intrauterine growth.

In this retrospective birth cohort study among the Chinese population, we aimed to investigate the associations of maternal iron nutrition during pregnancy, combining iron supplementation, dietary iron, and iron status, with fetal intrauterine growth parameters measured by fetal ultrasound examinations in the second and third trimesters.

Materials and methods

Study design and participants

A retrospective birth cohort study was conducted in the First Affiliated Hospital of Xi'an Jiaotong University in Xi'an City, Northwest China. Pregnant women who underwent regular antenatal checks and delivered at the study hospital were invited to participate in this study when they were waiting for delivery in the obstetric department from June 2014 to December 2015. Women with gestational complications such as diabetes, hypertension, and thyroid dysfunction were not recruited in the study. Among the 613 participants with live births, we excluded those if they had multiple pregnancies ($N=24$), fetuses with birth defects ($N=63$), or less than two fetal ultrasound examinations in the second and third trimesters (> 12 gestational weeks) in the study hospital ($N=44$). A total of 482 pregnant women were finally included to analyze the association between maternal iron nutrition during pregnancy and fetal intrauterine growth (Figure S1). Each participant provided a written informed consent before inclusion. The study was approved by the Ethics Committee of Xi'an Jiaotong University Health Science Center (No. 2021–28).

Data collection

Trained investigators conducted a face-to-face survey with a standardized questionnaire to collect maternal information in pregnancy when pregnant women were waiting for delivery in the hospital. The collected information on dietary supplements included type/ brand, lasting day, and the amount of all dietary supplements participants used during each trimester of pregnancy. Daily supplemental iron intake was calculated by multiplying the iron content of each reported supplement and the number of supplement tablets taken daily. Maternal diets during the whole pregnancy were collected by a 111-item semi-quantitative food frequency questionnaire (FFQ). This FFQ was established on the basis of a validated FFQ used for pregnant women in Northwest China [25]. Dietary habits of pregnant women tended to be stable from early to late pregnancy [26]; thus it seems to be reasonable and convenient to survey their diets throughout pregnancy at one time [13, 27, 28]. Pregnant women reported the consumption frequency of food in pregnancy according to 8 predefined categories, and recalled the portion size with the help of the food portion size map. We calculated the daily intake of dietary iron during pregnancy with reference to the Chinese Food Composition Tables [29, 30]. The recommended nutrient intake for dietary iron is 29 mg/d among Chinese pregnant women according to the latest Chinese Dietary Reference Intakes [31]. Blood samples of pregnant women were conveniently collected before delivery, and the concentration of serum ferritin (SF) was determined by enzyme linked immunosorbent assay (KingMed Diagnostics, China). The concentrations of hemoglobin (Hb) and SF were also measured in the antenatal check among pregnant women, and these values were extracted from the medical records.

Professional physicians in the study hospital conducted fetal ultrasound examinations using the GE voluson E8 ultrasound machine (GE Health care Austria GmbH &CoOG, Zipf, Austria). These physicians adhered to the standard quality criteria for the placement of calipers and ellipses with proper visualization of landmarks in all fetal planes, following protocols from the INTERGROWTH-21st Project [32]. Fetal intrauterine growth parameters including BPD, FL, and AC in the second and third trimesters were measured three times and the means were finally recorded. EFW was calculated in grams using the Hadlock formula [33] on the basis of BPD, FL, and AC. Gestational week was calculated according to the self-reported last menstrual period, and confirmed using the crown-rump length measured by ultrasound during early pregnancy. The z-scores of fetal intrauterine growth parameters were calculated according to INTERGROWTH-21st reference standards for fetal growth [34].

Covariates

The general information of participants were obtained through a standardized questionnaire. The study covariates included maternal age, residence, education, preconception BMI, fetal sex, and anemia during pregnancy. Preconception weight and height were reported by pregnancy women to calculate BMI. Preconception BMI was categorized into three groups with the cutoffs of 18.5 kg/m^2 and 24.0 kg/m^2 according to the Chinese criteria [35]. Women with hemoglobin concentration $<$ 110 g/L were diagnosed with anemia in pregnancy.

Statistical analysis

For the baseline characteristics of the study sample, continuous variables were expressed as means (SD) and categorical variables as frequencies (percentages). The distribution of fetal intrauterine growth parameters (BPD, FL, AC, and EFW) in the second and third trimesters at the 25th, 50th, and 75th percentiles were described. The associations of iron supplementation, dietary iron intake, and total iron intake during pregnancy with fetal intrauterine growth parameters (BPD, FL, AC, and EFW) in the second and third trimesters were evaluated by fitting simultaneous-quantile regression models with bootstrapped standard errors at the 25th, 50th, and 75th percentiles in the distribution of each outcome. Using a quantile regression approach, we examined whether iron supplementation and iron intake during pregnancy had distinct effects on the median and extremes of the distributions of BPD, FL, AC, and EFW. The estimation of coefficients at a given percentile was based on the reduction of the median absolute deviation. We also drew quantile regression plots to visually show the regression coefficients at these quantiles and their 95% confidence intervals, and to make an intuitive comparison with the coefficients of the least square method. In the adjusted quantile regression models, the study covariates included maternal age, residence, education, preconception BMI, fetal sex, and anemia during pregnancy. The linear regression model was used to analyze the associations between iron status (SF and Hb) in different trimesters and fetal intrauterine growth parameters in the second and third trimesters, with adjustment for maternal age and preconception BMI. The study covariates were selected according to their associations with fetal growth and the exposures and the change in estimates over 10% [36]. The analyses for SF were not adjusted for inflammation because of the unavailable information.

All analyses were performed using Stata version 15 (StataCorp, College Station, TX, USA). A two-sided $P < 0.05$ was considered as statistically significant.

Results

Baseline characteristics of the study sample

Table 1 presents the baseline characteristics of the study sample. Among the 482 pregnant women, the mean age was 29.0 (SD: 3.9) years, 70.3% resided in urban areas, 83.0% had the educational level of college or above, and 76.7% were primiparous. The mean preconception BMI was 21.3 (SD: 2.8) kg/m^2. Participants reported taking iron supplementation in pregnancy accounted for 54.8%, and those with iron supplements in the first, second, and third trimesters accounted for 19.1%, 40.3%, and 37.8% of the sample, respectively. The mean dietary iron intake in pregnancy was 22.1 (SD: 12.2) mg/d, and pregnant women had dietary iron intake below the recommended nutrient intake of 29 mg/d accounted for 76.1%. The mean total iron intake from diets and supplements in pregnancy was 32.6 (SD: 21.2) mg/d. Anemic pregnant women accounted for 12.2%. Male fetuses accounted for 55.3%. The distributions of fetal intrauterine growth parameters in the second and third trimesters are detailed in Table S1. The mean gestational weeks of fetal ultrasound examinations in the second and third trimesters were 21.3 (SD: 4.2) and 36.7 (SD: 3.1) weeks, respectively. According to the international standards by gestational age, the median z-scores for BPD, FL, and AC were slightly lower than the expected average values, while the median z-score for EFW was close to the expected average value. At the 25th percentile of the distribution for each fetal intrauterine growth parameter, z-scores were all below -0.05, ranging from -2.1 to -0.6.

Table 1 Baseline characteristics of the study sample (*N* = 482)

Characteristics	Mean (SD)/n (%)[a]
Maternal socio-demographic characteristics	
Maternal age, years	29.0 (3.9)
< 30	311 (64.5)
≥ 30	171 (35.5)
Residence	
Urban	339 (70.3)
Rural	143 (29.7)
Maternal education	
Junior school or below	35 (7.3)
High school	47 (9.8)
College or above	400 (83.0)
Parity	
0	369 (76.7)
≥ 1	112 (23.3)
Preconception BMI, kg/m.^{2}	21.3 (2.8)
< 18.5	63 (13.1)
18.5 ~ 23.9	334 (69.3)
≥ 24	85 (17.6)
Maternal iron nutrition during pregnancy	
Iron supplementation in the first trimester	
Yes	92 (19.1)
No	390 (80.9)
Iron supplementation in the second trimester	
Yes	194 (40.3)
No	288 (59.8)
Iron supplementation in the third trimester	
Yes	182 (37.8)
No	300 (62.2)
Supplemental iron intake in pregnancy, mg/d	10.5 (15.9)
Dietary iron intake in pregnancy, mg/d	22.1 (12.2)
< 29	367 (76.1)
≥ 29	115 (23.9)
Total iron intake (dietary iron + supplemental iron) in pregnancy, mg/d	32.6 (21.2)
Anemia in pregnancy	
Yes	59 (12.2)
No	423 (87.8)
Fetal sex	
Male	256 (53.3)
Female	224 (46.7)

[a] Continuous variables were expressed as means (SD), and categorical variables as frequencies (percentages)

On the other hand, values at the 75th percentile were above 0, except for -0.4 for BPD z-score in the second trimester and -0.04 for AC z-score in the third trimester.

Associations between maternal iron intake during pregnancy and fetal intrauterine growth

Maternal iron supplementation in the first trimester was associated with a 0.21 (95%CI = 0.07–0.34) increase in median z-score for BPD in the second trimester, while no significant associations at other percentiles (Table 2 and Figure S2). Maternal iron supplementation in the second trimester were positively associated with BPD, FL, and AC at the 50th percentile and above, and with EFW between the 25th and 75th percentiles in the second trimester (Table 2 and Figure S3). Compared with those without iron supplementation in the second trimester, pregnant women with iron supplementation in the second trimester had 0.37 (95%CI = 0.24–0.49), 0.37 (95%CI = 0.26–0.48), 0.15 (95%CI = 0.04–0.26), and 0.52 (95%CI = 0.42–0.61) higher z-scores in fetal BPD, FL, AC, and EFW at the 50th percentile in the second trimester, respectively. Dietary iron intake in pregnancy was not associated with fetal intrauterine growth in the second trimester (Table 2). Total iron intake in pregnancy was positively associated with BPD and AC between the 50th and 75th percentiles, with FL at the 50th percentile and above, and with EFW between the 25th and 75th percentiles (Table 2 and Figure S4). Each 1 mg increase in total iron intake during pregnancy was associated with the increments of 0.0038 to 0.0106 in median z-scores for fetal intrauterine growth parameters in the second trimester.

Maternal iron supplementation in the first trimester was associated with 0.26 (95%CI = 0.06–0.45) and 0.24 (95%CI = 0.01–0.47) increases in z-scores for AC and EFW at the 25th percentile in the third trimester, respectively, and 0.31 (95%CI = 0.04–0.58) increase in median z-score for FL in the third trimester, while no significant associations at other percentiles (Table 3 and Figure S5). Maternal iron supplementation in the second trimester was associated with 0.23 (95%CI = 0.02–0.45) increase in median z-score for BPD in the third trimester, with the positive association also showed in the extreme high percentile (Table 3 and Figure S6). Iron supplementation in the third trimester and dietary iron intake in pregnancy was not associated with fetal intrauterine growth in the third trimester (Table 3). Total iron intake in pregnancy was positively associated with BPD at the 25th percentile, with AC between the 25th and 75th percentiles, with FL at the 75th percentile, and with EFW at the 50th percentile (Table 3 and Figure S7), with the increments ranging from 0.0032 to 0.0056.

Table 2 Associations between maternal iron intake during pregnancy and fetal intrauterine growth in the second trimester

Fetal intrauterine growth parameters in z-scores for gestational age[a]								
	Biparietal diameter		**Femur length**		**Abdominal circumference**		**Estimated fetal weight**	
Percentiles	**β (95%CI)**	***P***	**β (95%CI)**	***P***	**β (95%CI)**	***P***	**β (95%CI)**	***P***
Iron supplementation in the first trimester								
25th	0.38 (-0.10,0.86)	0.184	0.07 (-0.36, 0.49)	0.633	0.12 (-0.21, 0.44)	0.279	0.12 (-0.10, 0.34)	0.225
50th	0.21 (0.07,0.34)	0.003	-0.02 (-0.16, 0.11)	0.997	0.06 (-0.07, 0.20)	0.419	0.03 (-0.06, 0.12)	0.505
75th	0.01 (-0.12,0.15)	0.612	0.03 (-0.11, 0.17)	0.968	-0.02 (-0.10, 0.07)	0.928	-0.05 (-0.19, 0.09)	0.553
Iron supplementation in the second trimester								
25th	0.16 (-0.25,0.57)	0.399	0.25 (-0.18, 0.68)	0.490	-0.03 (-0.36, 0.29)	0.732	0.44 (0.20, 0.70)	< 0.001
50th	0.37 (0.24,0.49)	< 0.001	0.37 (0.26, 0.48)	< 0.001	0.15 (0.04, 0.26)	0.001	0.52 (0.42, 0.61)	< 0.001
75th	0.49 (0.37,0.61)	< 0.001	0.45 (0.34, 0.56)	< 0.001	0.31 (0.23, 0.40)	< 0.001	0.53 (0.38, 0.68)	< 0.001
Dietary iron intake in pregnancy								
25th	-0.0068 (-0.0147,0.0012)	0.108	-0.0086 (-0.0178, 0.0006)	0.088	-0.0038 (-0.0121, 0.0044)	0.293	-0.0023 (-0.0088, 0.0042)	0.496
50th	-0.0012 (-0.0069,0.0045)	0.718	-0.0029 (-0.0081, 0.0023)	0.696	-0.0005 (-0.0048, 0.0038)	0.815	0.0011 (-0.0027, 0.0049)	0.599
75th	0.0019 (-0.0049,0.0087)	0.551	-0.0017 (-0.0063, 0.0029)	0.441	-0.0013 (-0.0047, 0.0022)	0.489	0.0002 (-0.0047, 0.0051)	0.928
Total iron intake in pregnancy								
25th	0.0036 (-0.0026,0.0097)	0.278	0.0009 (-0.0070, 0.0088)	0.797	0.0001 (-0.0091, 0.0092)	0.988	0.0072 (0.0002, 0.0142)	0.038
50th	0.0048 (0.0019,0.0076)	0.002	0.0038 (0.0009, 0.0067)	0.013	0.0048 (0.0012, 0.0085)	0.004	0.0106 (0.0083, 0.0130)	< 0.001
75th	0.0056 (0.0019,0.0093)	0.005	0.0049 (0.0020, 0.0077)	< 0.001	0.0045 (0.0012, 0.0078)	0.022	0.0077 (0.0024, 0.0130)	0.004

[a] Biparietal diameter, femur length, abdominal circumference and estimated fetal weight z-scores for gestational age were calculated according to the INTERGROWTH 21st Project standards. Coefficients and 95% confidence intervals (95% CI) for each fetal intrauterine growth parameter were estimated using simultaneous-quantile regression models with bootstrapped standard errors for the 25th, 50th and 75th percentiles in the distribution. Analyses were adjusted for maternal education, residence, preconception BMI, fetal sex, and anemia during pregnancy. Iron supplementation in the first and second trimesters and dietary iron intake in pregnancy were mutually adjusted in the corresponding analyses

Associations between maternal iron status during pregnancy and fetal intrauterine growth

Maternal SF concentrations were 27.3 (SD: 11.9) μg/L, 21.0 (SD: 11.8) μg/L, and 20.7 (SD: 11.2) μg/L in the first, second, and third trimesters, respectively, and for Hb concentrations the values were 128.2 (SD: 2.8) g/L, 119.4 (SD: 8.4) g/L, and 112.6 (SD: 15.6) g/L, respectively. The relationships between maternal iron status and fetal intrauterine growth parameters are shown in Table 4 and Table 5. Maternal SF concentration in the first trimester was positively correlated with z-scores for all fetal intrauterine growth parameters (BPD, FL, AC, and EFW) in the second and third trimesters (all $P < 0.05$), and maternal Hb concentration in the first trimester was positively correlated with z-scores for FL, AC, and EFW in the second trimester (all $P < 0.05$). Maternal SF concentration in the second trimester was positively correlated with z-scores for FL, AC, and EFW in the second trimester and BPD and FL in the third trimester (all $P < 0.05$), and maternal Hb concentration in the second trimester was positively correlated with z-scores for all fetal growth parameters (BPD, FL, AC, and EFW) in the second trimester (all $P < 0.05$). No significant associations were found between maternal iron status (SF and Hb concentrations) in the third trimester and fetal intrauterine growth in the third trimester.

Discussion

In this retrospective birth cohort study, we found that pregnant women with iron supplementation in the first and second trimesters and with higher total iron intake from diets and supplements in pregnancy had higher values for fetal intrauterine growth parameters (BPD, FL, AC, and EFW). We also observed that maternal SF and Hb concentrations in the first and second trimesters were positively associated with fetal intrauterine growth. To our knowledge, this study is the first study to comprehensively explore the associations of maternal iron nutrition integrating iron supplementation, dietary iron, and iron status with fetal intrauterine growth.

Previous studies on fetal growth have often used physical measurements at birth as the outcomes. One recent study in UK showed that iron supplementation during pregnancy was positively associated with various birth sizes including birth weight, head circumference, and

Table 3 Associations between iron intake during pregnancy and fetal intrauterine growth in the third trimester

Fetal intrauterine growth parameters in z-scores for gestational age[a]								
	Biparietal diameter		**Femur length**		**Abdominal circumference**		**Estimated fetal weight**	
Percentiles	**β (95%CI)**	***P***	**β (95%CI)**	***P***	**β (95%CI)**	***P***	**β (95%CI)**	***P***
Iron supplementation in the first trimester								
25th	0.11 (-0.21, 0.43)	0.526	-0.01 (-0.37, 0.36)	0.967	0.26 (0.06, 0.45)	0.025	0.24 (0.01, 0.47)	0.048
50th	-0.02 (-0.28, 0.23)	0.881	0.31 (0.04, 0.58)	0.045	0.21 (-0.04, 0.46)	0.083	0.21 (-0.04, 0.46)	0.104
75th	0.06 (-0.25, 0.38)	0.701	0.01 (-0.22, 0.23)	0.954	0.11 (-0.18, 0.39)	0.427	0.08 (-0.13, 0.28)	0.389
Iron supplementation in the second trimester								
25th	0.27 (-0.06, 0.59)	0.123	0.11 (-0.14, 0.37)	0.435	-0.11 (-0.33, 0.10)	0.309	-0.06 (-0.25, 0.13)	0.545
50th	0.23 (0.02, 0.45)	0.020	-0.07 (-0.35, 0.21)	0.617	0.03 (-0.16, 0.21)	0.770	0.09 (-0.15, 0.33)	0.358
75th	0.24 (-0.06, 0.53)	0.122	0.07 (-0.17, 0.31)	0.556	0.15 (-0.07, 0.38)	0.218	0.16 (-0.05, 0.36)	0.072
Iron supplementation in the third trimester								
25th	0.06 (-0.26, 0.37)	0.754	0.06 (-0.20, 0.33)	0.633	0.09 (-0.11, 0.28)	0.375	0.06 (-0.12, 0.24)	0.527
50th	-0.15 (-0.34, 0.05)	0.170	0.11 (-0.15, 0.38)	0.367	0.08 (-0.10, 0.26)	0.361	0.04 (-0.14, 0.23)	0.671
75th	-0.12 (-0.40, 0.16)	0.455	0.12 (-0.08, 0.32)	0.179	0.09 (-0.10, 0.27)	0.349	-0.08 (-0.28, 0.12)	0.472
Dietary iron intake in pregnancy								
25th	-0.0019 (-0.0127, 0.0087)	0.746	0.0012 (-0.0096, 0.0121)	0.814	0.0009 (-0.0074, 0.0091)	0.814	0.0013 (-0.0043, 0.0070)	0.633
50th	-0.0034 (-0.0115, 0.0047)	0.492	0.0003 (-0.0072, 0.0077)	0.941	0.0006 (-0.0049, 0.0062)	0.808	0.005 (-0.0025, 0.0124)	0.226
75th	-0.0008 (-0.0109, 0.0091)	0.871	0.003 (-0.0056, 0.0116)	0.418	0.0026 (-0.0055, 0.0108)	0.505	0.0013 (-0.0073, 0.0099)	0.746
Total iron intake in pregnancy								
25th	0.0048 (0.0007, 0.0089)	0.026	0.0029 (-0.0023, 0.0081)	0.216	0.0034 (-0.0012, 0.0081)	0.117	0.0027 (-0.0008, 0.0063)	0.138
50th	0.0008 (-0.0030, 0.0045)	0.648	0.0041 (-0.0013, 0.0095)	0.149	0.0032 (0.0001, 0.0063)	0.037	0.0056 (0.0012, 0.0100)	0.020
75th	-0.0003 (-0.0053, 0.0046)	0.900	0.0038 (0.0004, 0.0071)	0.043	0.0054 (0.0012, 0.0096)	0.023	0.0034 (-0.0004, 0.0073)	0.070

[a] Biparietal diameter, femur length, abdominal circumference and estimated fetal weight z-scores for gestational age were calculated according to the INTERGROWTH 21st Project standards. Coefficients and 95% confidence intervals (95% CI) for each fetal intrauterine growth parameter were estimated using simultaneous-quantile regression models with bootstrapped standard errors for the 25th, 50th and 75th percentiles in the distribution. Analyses were adjusted for maternal education, residence, preconception BMI, fetal sex, and anemia during pregnancy. Iron supplementation in the first, second, and third trimesters and dietary iron intake in pregnancy were mutually adjusted in the corresponding analyses

Table 4 Associations between maternal iron status in different trimesters and fetal intrauterine growth in the second trimester

	Fetal intrauterine growth parameters in z-scores for gestational age[a]			
	Biparietal diameter	**Femur length**	**Abdominal circumference**	**Estimated fetal weight**
Iron status in the first trimester (*n* = 15)				
Serum ferritin, μg/L	0.03 (0.01, 0.05)	0.06 (0.05, 0.07)	0.05 (0.03, 0.06)	0.04 (0.03, 0.04)
β (95% CI)	0.008	0.009	< 0.001	< 0.001
P				
Hemoglobin, g/L				
β (95% CI)	0.05 (-0.10, 0.19)	0.22 (0.04, 0.40)	0.31 (0.30, 0.32)	0.15 (0.05, 0.25)
P	0.51	0.02	< 0.001	0.007
Iron status in the second trimester (*n* = 24)				
Serum ferritin, μg/L				
β (95% CI)	0.02 (-0.01, 0.05)	0.03 (0.01, 0.05)	0.05 (0.02, 0.09)	0.05 (0.03, 0.07)
P	0.12	0.007	0.004	< 0.001
Hemoglobin, g/L				
β (95% CI)	0.05 (0.01, 0.09)	0.04 (0.01, 0.07)	0.05 (0.01, 0.11)	0.06 (0.03, 0.09)
P	0.01	0.02	0.04	< 0.001

[a] Biparietal diameter, femur length, abdominal circumference and estimated fetal weight z-scores for gestational age were calculated according to the INTERGROWTH 21st Project standards. The linear regression models were used for the analyses, with adjustment for maternal age and preconception BMI

Table 5 Associations between maternal iron status in different trimesters and fetal intrauterine growth in the third trimester

	Fetal intrauterine growth parameters in z-scores for gestational age[a]			
	Biparietal diameter	**Femur length**	**Abdominal circumference**	**Estimated fetal weight**
Iron status in the first trimester (*n* = 15)				
Serum ferritin, μg/L				
β (95% CI)	0.03 (0.02, 0.05)	0.06 (0.03, 0.10)	0.06 (0.04, 0.09)	0.06 (0.04, 0.08)
P	0.001	0.001	< 0.001	< 0.001
Hemoglobin, g/L				
β (95% CI)	-0.08 (-0.21, 0.06)	0.16 (-0.13, 0.45)	0.18 (-0.08, 0.44)	0.20 (-0.3, 0.44)
P	0.22	0.25	0.15	0.09
Iron status in the second trimester (*n* = 24)				
Serum ferritin, μg/L				
β (95% CI)	0.05 (0.03, 0.07)	0.02 (0.01, 0.03)	0.01 (-0.02, 0.03)	0.02 (-0.01, 0.04)
P	< 0.001	0.04	0.47	0.08
Hemoglobin, g/L				
β (95% CI)	0.08 (-0.05, 0.11)	0.02 (-0.01, 0.05)	0.01 (-0.03, 0.03)	0.01 (-0.02, 0.04)
P	0.07	0.08	0.69	0.50
Iron status in the third trimester (*n* = 12)				
Serum ferritin, μg/L				
β (95% CI)	0.01 (-0.02, 0.03)	0.01 (-0.02, 0.02)	0.03 (-0.01, 0.07)	0.03 (-0.01, 0.06)
P	0.65	0.52	0.08	0.12
Hemoglobin, g/L				
β (95% CI)	-0.02 (-0.03, 0.01)	-0.01 (-0.04, 0.02)	-0.01 (-0.05, 0.03)	-0.01 (-0.05, 0.03)
P	0.18	0.39	0.50	0.51

[a] Biparietal diameter, femur length, abdominal circumference and estimated fetal weight z-scores for gestational age were calculated according to the INTERGROWTH 21st Project standards. The linear regression models were used for the analyses, with adjustment for maternal age and preconception BMI

BMI [37]. The significantly positive association of maternal iron supplementation in pregnancy with birth weight was also found in prior studies among the Chinese populations [13, 38]. One systematic review concluded that pregnant women taking iron supplementation had a lower risk of anemia during pregnancy, higher Hb concentration from late pregnancy to delivery, and lower risks of low birth weight and preterm birth [39]. Total iron intake from diets and supplements during pregnancy was also reported to be associated with the increased birth weight [16]. As for iron status and fetal growth, maternal low concentrations of SF and Hb in pregnancy were observed to increase the risks of low birth weight and small for gestational age among newborns in the prior studies [40, 41]. Results from these previous studies were consistent with the findings of our study about fetal intrauterine growth associated with maternal iron supplementation, total iron intake, and iron status during pregnancy. Our study focused on fetal intrauterine growth parameters (BPD, FL, AC, and EFW) in association with maternal iron intake and iron status in different trimesters, and the findings suggested that maternal iron nutrition in the first and second trimesters had positive effects on fetal intrauterine growth. Previous studies have also showed that anemia/iron deficiency in early pregnancy or even in the preconception stage is a risk factor for impaired fetal growth [40, 42], highlighting the importance of maternal iron supplementation as early as possible to improve fetal growth.

There are limited studies investigating iron nutrition in pregnancy and fetal growth in utero [21–23]. Consistent with the results in our study, one cohort study in Ireland recently reported that dietary iron intake during pregnancy was not significantly associated with fetal AC and EFW between 20 and 34 gestational weeks [23]. Another cohort study in South Korea also observed no association of dietary iron intake in pregnancy with fetal intrauterine growth parameters but significant associations of iron supplementation in pregnancy with fetal BDP and AC at mid pregnancy [22], which were in line with the results of the present study. One recent randomized clinical trial in Spain found that 80 mg/d iron supplementation among pregnant women with initial Hb between 110–130 g/L in early pregnancy increased the risks of fetal FL and EFW < 10th percentile at the third trimester and fetal head circumference > 90th percentile at the second trimester [21], indicating the importance of adjusting prenatal iron supplementation according to the initial

Hb level to achieve optimal fetal growth. Moreover, people with different genetic backgrounds may respond distinctly to iron intake and iron status. For example, the interaction of maternal iron intake and gene was reported to influence birth weight [43]. Therefore, further studies integrating maternal initial iron status in early pregnancy with genetic backgrounds to explore the effects of iron nutrition on fetal intrauterine growth are warranted.

Iron is necessary for DNA synthesis, various enzymatic processes, and mitochondrial energy generation [10], which may have effects on the health of pregnant women and their fetuses. Maternal iron supplementation in pregnancy was reported to increase maternal and fetal iron status and improve placental function to further promote fetal growth [44]. In the present study, pregnant women had inadequate iron intake from food, with 76.1% of them below the recommended nutrient intake, which makes iron supplementation more necessary to meet the physiologic iron requirement in pregnancy. However, only 54.8% of participants took iron supplementation during pregnancy in this study, with 19.1%, 40.3%, and 37.8% in the three different trimesters, respectively, and the mean supplemental iron intake in pregnancy was only 10.5 mg/d. Therefore, the possible negative effects of excessive iron such as oxidative stress and competitive absorption with other minerals reported in the previous studies [21, 22] may not occur among pregnant women in our study. The results of no association between dietary iron intake and fetal growth may be due to different absorption levels for different iron forms in food. For example, heme iron absorption is more efficient than non-heme iron [45]. It is also possible that pregnant women with better iron status may absorb less iron because of the increasing hepcidin [46], which further influence the observed association between dietary iron and fetal growth. Further studies on the effects of different sources of dietary iron intake and different iron status on fetal growth may help elucidate these topics.

This study provides valuable evidence about the association between iron nutrition during pregnancy and fetal intrauterine growth. However, some limitations should be discussed. First, recall bias cannot be ruled out because maternal data during pregnancy was retrospectively collected when participants awaiting delivery, although prior studies showed that mothers could report events during pregnancy well after years [47, 48]. Second, measurement errors cannot be excluded because fetal intrauterine growth parameters were measured through ultrasound scans, although there were standard protocols and strict training for ultrasound physicians in the study hospital [49]. Third, confounding bias cannot be disregarded because of other unmeasured or unknown factors, and the real causal relationship cannot be inferred because of the observational design. Finally, the generalization of the findings may be limited by the small sample size and the specific study hospital in Northwest China. Therefore, the results of this study should be interpreted with caution.

Conclusions

In summary, this study found that maternal iron supplementation and iron status in the first and second trimesters were positively associated with fetal intrauterine growth parameters including BPD, FL, AC, and EFW. These findings highlight the importance of improving maternal iron nutrition in the first and second trimesters to promote fetal intrauterine growth. It remains to investigate the real causal relationship between maternal iron nutrition during pregnancy and fetal intrauterine growth among different populations, especially integrating initial iron status with genetic backgrounds.

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

JY and XT contributed to study concept and design. JY and QC drafted the initial manuscript. JY, QC, DC, XL, and SD conducted statistical analyses. JY, QC, DC, XL, and SD collected the data. JY and XT revised the manuscript. All authors have read and approved the final version of the manuscript.

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Data availability

The datasets in this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Xi'an Jiaotong University Health Science Center (No.2021–28). Informed consent was obtained from all participants in the present study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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