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Maternal iron deficiency assessed by serum ferritin and birth outcomes in mainland China

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Iron deficiency is prevalent among pregnant women because of the increased maternal iron requirements. Uncorrected maternal iron deficiency can lead to adverse neurodevelopmental outcomes in neonates. Therefore, the aim of this study was to assess serum ferritin concentration and prevalence of iron deficiency among pregnant women in Jiangsu, China. Within a cohort study, pregnant women were followed up from 2nd trimester of pregnancy until their labour. They were assessed for iron status in 2nd and 3rd trimesters using serum ferritin. In addition, neonatal APGAR score and birth weight were assessed in order to determine if maternal iron deficiency was associated with these neonatal outcomes. A total of 1688 pregnant women were followed up until their labour. The mean age of participants was 29 ± 4 years and 54.0% of them were multigravidas. Mean serum ferritin concentration in 2nd trimester was significantly higher than 3rd trimester (59.9 vs. 22.2 ng/mL) ($P < 0.001$). The prevalence of iron deficiency using serum ferritin concentration cut-off of < 15 ng/mL in 2nd and 3rd trimesters was 11.9% and 37.4%, respectively ($P < 0.05$). Maternal iron deficiency as assessed by serum ferritin concentration in 2nd and 3rd trimesters of pregnancy was not associated with neonatal outcomes (all $P > 0.05$). Our study reported that increased prevalence of maternal iron deficiency in 3rd trimester, suggesting that screening and supplementation of at-risk pregnancies can be used as a preventive strategy to tackle the issue. Consideration should be given to ensure adequate maternal iron status through pregnancy.

Keywords Iron deficiency, Serum ferritin, Haemoglobin, Anaemia, Pregnant women

Iron deficiency is one of the major public health issues worldwide, which represents one of top nonfatal diseases[1]. Although iron deficiency is prevalent especially in pregnant women, it is often overlooked in clinical practice[2]. Anaemia is a late presentation of iron deficiency. Iron deficiency can be present in an individual before anaemia appears as iron is preferentially used for erythropoiesis by the body[2]. Thus perinatal iron deficiency can have adverse effect even without presence of maternal anaemia. For example, iron deficiency in pregnant women is associated with an increased risk of morbidity and foetal death[3].

The prevalence of global iron deficiency varies significantly during pregnancy, ranging from 6.5 to 85%[4–8]. Although there is no gold standard for assessing iron deficiency in pregnant women, one of the commonly used biomarkers of iron deficiency in pregnant women include serum ferritin. A low serum ferritin concentration in pregnant women has been used to indicate iron deficiency, which is associated with fatigue and dizziness[9]. It is one of the most readily available and clinically useful biomarker for evaluating iron deficiency in populations[10]. In addition, serum ferritin has been proposed to be the most sensitive single test for assessing iron stores[11].

In China, due to the vast territory, there is a wide diversity of dietary habits, living environments, food and economy[12]. Therefore, the prevalence of iron deficiency among pregnant women in different provinces of China can vary significantly. The prevalence of maternal iron deficiency in China is estimated to be ~ 50%, which is higher than that of the USA, Canada and Australia[5,6,12]. In addition, there are inconsistent findings regarding the

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prevalence of maternal iron deficiency and its relationship with adverse neonatal outcomes. In 2015, the Chinese government introduced the universal two-child policy, which was aimed to improve the stagnant population growth by targeting eligible women of reproductive age with a previous delivery[13]. The implementation of the universal two-child policy has been reported to be associated with increased birth rate[13]. In addition, women who are having a second child are mostly above 35 years of age and multiparous, making them more prone to iron deficiency[13]. Therefore, it is unclear if the prevalence of maternal iron deficiency would exacerbate following the implementation of the universal two-child policy.

Therefore, the aim of this study was to assess the prevalence of maternal iron deficiency using serum ferritin concentration and its relationship with neonatal outcomes in a sample of mother-and-newborn pairs from Jiangsu Province, China following the implementation of the universal two-child policy.

Methods

Study population and setting

This cohort study included pregnant women delivered in Northern Jiangsu People's Hospital, Yangzhou, Jiangsu, China between January 2017 and December 2017. Eligible women during their 2nd trimester of pregnancy who were healthy and aged ≥ 18 years were recruited into our study. Only pregnant women with a normal singleton pregnancy and had a live birth after labour were included in the final analysis. Informed consent was obtained from pregnant women prior to study enrolment. The Ethics Committee of the Northern Jiangsu People's Hospital had approved our study protocol (reference no. 2018063), which was also compiled with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Our study was conducted according to the STROBE checklist for the cohort studies.

Socio-demographic data collection and anthropometric measurement

Data on maternal socio-demographics including their age, height, weight, weeks of gestation and number of previous pregnancies were collected by the trained medical staff when pregnant women attended their antenatal visits. Their maternal body mass index (BMI) was calculated and classified according to the criteria for Chinese populations by the Working Group on Obesity in China: underweight, < 18.5 kg/m^2; normal weight, 18.5–23.9 kg/m^2; overweight 24.0–27.9 kg/m^2; obese, ≥ 28.0 kg/m^2[14–16].

Biochemical measurements

Pregnant women were asked to provide an overnight fasting blood sample (6 mL) for the determination of serum ferritin concentration using red-top tubes. The normal reference range of serum ferritin concentration was between 13 and 150 ng/mL. Since there are some variations in serum ferritin thresholds to define maternal iron deficiency, we included the commonly used thresholds of serum ferritin for categorising the severity of iron deficiency: < 15 ng/mL, severe iron depletion; 15 to < 30 ng/mL, modest iron depletion; iron sufficiency ≥ 30 ng/mL, respectively[11,17,18]. In addition, serum ferritin concentration of < 15 ng/mL was used to indicate iron deficiency as recommended by WHO[19,20]. Serum ferritin concentration of pregnant women was determined by using a Roche Cobas 8000 Modular Analyser Series at the premises of the Northern Jiangsu People's Hospital Affiliated to Yangzhou University. The APGAR score at 10-minute (min) was also measured in neonates. Neonates with a birth weight of < 2500 g or ≥ 4000 g were categorised as LBW or large for gestational age (LGA), respectively[19,21].

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics for Windows ver. 25 (IBM SPSS Statistics for Windows, IBM Corporation, Armonk, NY, USA). Descriptive statistics were presented as percentages for categorical variable and means ± standard deviations (SD) for continuous variables. Comparisons of demographics and serum feritin concentration between women with different trimesters of pregnancy, BMIs and gravidity status were conducted using Chi-square tests for the categorical variables and general linear model (GLM) multivariate analyses for continuous variables. Logistic regression models were used to determine the binary outcome variables, including maternal iron deficiency status and LBW. A P-value < 0.05 was chosen to indicate statistical significance.

Results

Participant characteristics

A total of 1688 participants of Han ethnicity were recruited into the study and they were followed up until their labour. The mean age of participants was 29 ± 4 years (Table 1); obese participants was significantly older than that of overweight and normal BMI categories ($P < 0.001$) (Table 2). The average length of pregnancy was 39 ± 2 weeks and 46.0% of them were primigravida (Table 1). Mean serum ferritin concentration in 2nd trimester of pregnancy was significantly higher than that of 3rd trimester of pregnancy (59.9 ng/mL vs. 22.2 ng/mL) ($P < 0.001$). In addition, serum ferritin concentration in 2nd trimester of pregnancy was significantly associated with serum ferritin concentration in 3rd trimester of pregnancy ($r = 0.355$, $P < 0.001$). There was no difference in serum ferritin concentration between different age groups (i.e., 18–24 years, 25–29 years, 30–34 years, 35–39 years and 40–45 years) for 2nd trimester of pregnancy ($P = 0.723$). However, in 3rd trimester of pregnancy, there was a significant difference in mean serum ferritin concentration among pregnant women with different age groups (18–24 years, 19.4 ng/mL 25–29 years, 22.0 ng/mL; 30–34 years, 22.9 ng/mL; 35–39 years, 24.8 ng/mL; 40–45 years, 28.4 ng/mL) ($P = 0.006$).

The prevalence of iron deficiency using serum ferritin concentration cut-off of < 15 ng/mL in 2nd and 3rd trimesters of pregnancy was 11.9% and 37.4%, respectively ($P < 0.05$).

	Values
Age (years)	29 ± 4
Average length of pregnancy (gestational age at birth) (weeks)	39 ± 2
Primigravidas, n (%)	776 (46.0)
Serum ferritin concentration (ng/mL)	
2nd trimester[1]	59.9 ± 52.1
3rd trimester[2]	22.2 ± 14.1
Prevalence of iron deficiency using serum ferritin of < 15 ng/mL cut-off, n (%)	
2nd trimester[1]	160 (11.9)
3rd trimester[2]	427 (37.4)
Prevalence of moderate iron deficiency using serum ferritin of 15 to < 30 ng/mL cut-off, n (%)	
2nd trimester[1]	278 (20.6)
3rd trimester[2]	452 (39.5)
Neonatal weight (g)	3339 ± 462
Prevalence of LBW, *n (%)*	60 (3.6)
Prevalence of LGA, *n (%)*	100 (5.9)
Neonatal APGAR score	9.99 ± 0.13

Table 1. Socio-demographic characteristics and biochemical results of participants ($n = 1688$). [1]$n = 1349$ [2]$n = 1143$

	BMI ($n = 1688$)			
	Normal ($n = 277$)	Overweight ($n = 830$)	Obese ($n = 581$)	*P*-value
Age (years)	28 ± 4	28 ± 4	29 ± 5	**< 0.001**
Average length of pregnancy (gestational age at birth) (weeks)	39 ± 2	39 ± 2	39 ± 2	0.997
Weight (kg)	60 ± 5	68 ± 5	80 ± 9	**< 0.001**
BMI	23 ± 1	26 ± 1	31 ± 3	**< 0.001**
2nd trimester of pregnancy[1]				
Serum ferritin concentration (ng/mL)	64.2 ± 52.8	58.4 ± 49.5	60.0 ± 55.3	0.365
Prevalence of iron deficiency using serum ferritin < 15 ng/mL cut-off, *n (%)*	18/222 (8.1)	83/670 (12.4)	59/457 (12.9)	0.161
3rd trimester of pregnancy[2]				
Serum ferritin concentration (ng/mL)	22.0 ± 12.7	21.4 ± 14.3	23.6 ± 14.5	0.070
Prevalence of iron deficiency using serum ferritin < 15 ng/mL cut-off, *n (%)*	72/202 (35.6)	227/572 (39.7)	128/369 (34.7)	0.259
Neonatal weight (g)	3142 ± 402	3325 ± 447	3454 ± 476	**< 0.001**
Prevalence of LBW, n (%)	17 (6.1)	26 (3.1)	17 (2.9)	**0.039**
Prevalence of LGA, n (%)	2 (0.7)	41 (4.9)	57 (9.8)	**< 0.001**
Neonatal APGAR score	9.98 ± 0.22	10.00 ± 0.05	9.99 ± 0.14	0.087
Prevalence of neonatal 10-min APGAR score < 5, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	n.d.

Table 2. Serum ferritin concentration by maternal BMI. n.d., not determined due to low cell count [1]$n = 1349$ [2]$n = 1143$ Significant values are in [bold]

Maternal serum ferritin concentration by maternal BMI

No difference in serum ferritin concentration of 2nd and 3rd trimesters of pregnancy among different BMI categories was reported (normal BMI: 64.2 ng/mL and 22.0 ng/mL, respectively; overweight: 58.4 ng/mL and 21.4 ng/mL, respectively; obese: 60.0 ng/mL and 23.6 ng/mL, respectively) ($P > 0.05$) (Table 2). In addition, no difference in the prevalence of maternal iron deficiency using serum ferritin cut-off of < 15 ng/mL for 2nd and 3rd trimesters of pregnancy among different BMI categories was reported ($P > 0.05$). Obese participants had a significantly higher neonatal weight (3454 g) than those in normal BMI and overweight (3142 g and 3325 g, respectively) ($P < 0.001$).

Maternal serum ferritin concentration by gravidity

No difference in mean serum ferritin concentration of 2nd and 3rd trimesters of pregnancy between primigravidas and multigravidas was reported ($P > 0.05$) (Table 3). Similarly, there was no difference in the prevalence of iron deficiency using serum ferritin cut-off of < 15 µg/L for 2nd and 3rd trimesters of pregnancy between primigravidas and multigravidas ($P > 0.05$).

	Total ($n=1688$)		
	Primigravida ($n=776$)	**Multigravida ($n=912$)**	***P*-value**
Age (years)	27 ± 3	30 ± 4	**<0.001**
Average length of pregnancy (gestational age at birth) (weeks)	39 ± 2	39 ± 2	0.990
2nd trimester of pregnancy[1]			
Serum ferritin concentration (ng/mL)	62.3 ± 49.9	57.7 ± 53.9	0.109
Prevalence of iron deficiency using serum ferritin < 15 ng/mL cut-off, *n (%)*	71/647 (11.0)	89/702 (12.7)	0.333
3rd trimester of pregnancy[2]			
Serum ferritin concentration (ng/mL)	22.6 ± 13.9	22.0 ± 14.3	0.460
Prevalence of iron deficiency using serum ferritin < 15 ng/mL cut-off, *n (%)*	176/497 (35.4)	251/646 (38.9)	0.233
Neonatal weight (g)	3317 ± 478	3359 ± 448	0.062
Prevalence of LBW, n (%)	34 (4.4)	26 (2.9)	0.091
Prevalence of LGA, n (%)	41 (5.3)	59 (6.5)	0.304
Neonatal APGAR score	9.99 ± 0.14	9.99 ± 0.12	0.830
Prevalence of neonatal 10-min APGAR score < 5, n (%)	0 (0.0)	0 (0.0)	n.d.

Table 3. Serum ferritin concentration by gravidity. n.d., not determined due to low cell count [1]$n=1349$ [2]$n=1143$ Significant values are in [bold]

	OR	95% CI	*P*-value
(A) Maternal iron deficiency as assessed by serum ferritin concentration in 2nd trimester of pregnancy			
BMI (kg/m^2)			
Normal	Reference		
Overweight	0.624	0.366, 1.064	0.083
Obese	0.595	0.342, 1.036	0.066
LBW			
No	Reference		
Yes	1.587	0.482, 5.222	0.447
Gravidity			
Primigravidas	Reference		
Multigravidas	0.849	0.609, 1.183	0.334
(B) Maternal iron deficiency as assessed by serum ferritin concentration in 3rd trimester of pregnancy			
BMI (kg/m^2)			
Normal	Reference		
Overweight	0.842	0.603, 1.174	0.311
Obese	1.043	0.728, 1.493	0.819
LBW			
No	Reference		
Yes	1.128	0.619, 2.058	0.694
Gravidity			
Primigravidas	Reference		
Multigravidas	0.863	0.677, 1.100	0.233

Table 4. Logistic regression analysis on related variables for.

Maternal iron deficiency and neonatal outcomes

The overall mean neonatal birth weight was 3339 ± 462 g (Table 1). The prevalence of LBW and LGA was 3.6% and 5.9%, respectively. Mean APGAR score at 10 min was 9.99 ± 0.13. Maternal iron deficiency as assessed by serum ferritin concentration in 2nd and 3rd trimesters of pregnancy was not associated with neonatal outcomes (including LBW) (all $P>0.05$) (Table 4). Also, no difference in the body weight of mothers who had serum ferritin < 30 ng/ml (iron deficient) to those of neonates born to iron sufficient mothers.

Discussion

Iron deficiency is one of the most common nutrient deficiencies affecting over 30% of the world's population (~ 2 billion people)[22,23]. Iron deficiency is prevalent in both developed and developing countries, especially

among pregnant women[2,24]. It occurs when dietary iron cannot meet the physiologic iron requirements; iron deficiency worsens during pregnancy because of higher iron requirements which are needed for foetal development and growth[24].

The foetal and early postnatal periods are regarded as a sensitive and critical period because these periods are characterised by a rapid brain development, high nutritional requirement and high level of neuronal plasticity[25]. A systematic review by Janbek et al. suggested that maternal iron deficiency in 3rd trimester of pregnancy is associated with a higher risk of developing neurodevelopmental impairment[26]. In addition, the presence of iron deficiency anaemia during pregnancy is associated with a higher risk of APGAR score < 5 at 1 min and LBW in neonates[27].

In 2015, the Chinese government introduced the universal two-child policy to address the declining birthrate and rapidly aging population[13]. Women planning a second child and those already pregnant are likely to increase their use of maternal health services, which could result in earlier detection and treatment of maternal iron deficiencies. In addition, successful pregnancies without adequate recovery time in between can deplete the maternal iron stores, leading to increased risk of anaemia. This is because having a second child could mean a greater dietary demand for iron over a shorter period. Therefore, our study focused on assessing the prevalence of iron deficiency using serum ferritin concentration among a sample of mother-and-newborn pairs in Jiangsu, China following the implementation of universal two-child policy, and identifying if any neonatal outcomes were associated with maternal iron deficiency. Our study reported that the prevalence of iron deficiency in 3rd trimester of pregnancy was significantly higher than that of 2nd trimester of pregnancy when using serum ferritin cut-offs of < 15 ng/mL ($P < 0.05$). In addition, serum ferritin concentration of pregnant women in our study significantly decreased from 59.9 ng/mL in 2nd trimester of pregnancy to 22.2 ng/mL in 3rd trimester of pregnancy ($P < 0.05$). One possible reason for the decrease in maternal serum ferritin concentration in 3rd trimester of pregnancy was due to the acquisition of iron by foetus in 3rd trimester of pregnancy[28]. Therefore, the foetal iron concentration is maintained at the expense of the maternal iron metabolism and storage[28].

Our study reported that the prevalence of iron deficiency in 2nd and 3rd trimesters of pregnancy was 11.9% and 37.4%, respectively. A study by Loy et al.[8] reported that only 7% of pregnant women in Singapore had a serum ferritin concentration of < 15 ng/mL, which was lower than that of our study. On the other hand, our study reported that the prevalence of moderate iron deficiency in 2nd and 3rd trimesters of pregnancy was 20.6% and 39.5%, respectively. Our prevalence of moderate maternal iron deficiency was lower than other countries in Asia including Singapore. The prevalence of moderate iron deficiency assessed by plasma ferritin concentration in Singaporean pregnant women at 26–28 weeks of gestation was 67.0%[8]. However, the high proportion of pregnant women with moderate iodine deficiency in our study warrants further investigation, especially for subsequent clinical and biochemical consequences among mother-and–newborn pairs.

Although multiparity is associated with iron depletion in pregnant women[8], our study did not find any difference in mean serum ferritin concentration of 2nd and 3rd trimesters of pregnancy between primigravidas and multigravidas ($P > 0.05$). It is possible that multigravidas who had a better understanding of iron nutrition during pregnancy consumed more poultry, egg and meat to improve their iron status. However, this speculation needs to be validated in larger studies which include the use of dietary assessment to assess iron status in pregnant women.

Iron deficiency can be assessed by several biomarkers of iron status[29]. One of the biomarkers of iron status is serum ferritin concentration. Under normal conditions, iron status can be adequately assessed by serum ferritin concentration. However, the serum ferritin concentration cut-off used to diagnose maternal iron deficiency varies[7,20]. For example, according to the UK guidelines on the management of maternal iron deficiency, Pavord et al. reported that serum concentration cut-off of < 15 ng/mL can be used to diagnose iron deficiency[11]. This cut-off can also be used to assess maternal iron deficiency in all stages of pregnancy and indicate the presence of iron deficiency anaemia[30]. Pregnant women with a serum ferritin concentration of < 30 ng/mL should seek for medical treatment[11]. However, unselected routine screening of serum ferritin to assess maternal iron deficiency is not recommended because this will increase the healthcare cost, especially in resource-limited settings[11,18]. In addition, high cost of biochemical tests is needed to accurately assess iron status in pregnant women[18].

Our study had a number of strengths. Our study was designed as a cohort study, where pregnant women were followed up until they had their deliveries. In addition, our study was one of the first studies to investigate the prevalence of iron deficiency in pregnant women after the universal two-child policy was introduced in 2015 by the Chinese government. The inclusion of APGAR score for assessing the health of neonates was also another strength of our study because there are limited studies that had determine neonatal APGAR score in relation to maternal iron status. Although there were a small number of participants missed their follow-up antenatal visits either in 2nd or 3rd trimesters of pregnancy, they were still followed up until they went into labour. Therefore, their delivery outcomes were recorded and included in our data analysis.

One limitation of our study was that similar to the routine clinical assessment in some hospitals, no assessment of haemoglobin and inflammation biomarkers including C-reactive protein (CRP) and transferrin receptors was conducted in pregnant women[8]. Our study could have been strengthened by these measurements to provide a more comprehensive assessment of inflammation. Since serum ferritin concentration can be elevated in the presence of inflammation and chronic low-grade inflammation is associated with pregnancy, the prevalence of maternal iron deficiency in our study might be underestimated because of the lack of data on inflammatory markers[20,31,32]. Therefore, normal serum ferritin concentration does not exclude the possibility of maternal iron deficiency and there is a significant intraindividual variation in serum ferritin concentration[33,34]. In addition, it is possible that the expansion of plasma volume might play an important role in the interpretation of serum ferritin concentration during pregnancy. This is because serum ferritin concentration decreases as a result of hemodilution during pregnancy (a decrease in hematocrit (Hct)) especially in 2nd trimester and continues to decrease until 30 weeks of pregnancy[35]. However, if hemodilution is suggested as the cause for fall of serum

ferritin in 3rd trimester, it should have been more in second trimester[35]. There have been several guidelines published with respect to the serum ferritin cut-off for assessing iron deficiency[36]. In addition, other biomarkers of iron status including hepcidin and transferrin saturation could be assessed for a better determination of iron status, particularly in 3rd trimester of pregnancy. Therefore, our findings need to be interpreted cautiously.

In addition, studying the impact of iron deficiency on quality of life among pregnant women might have strengthened the study findings and added more to our understanding on the public health issue. The maternal use of iron supplements (dose and time of administration) and dietary iron intake should also be assessed in order to obtain a comprehensive assessment of iron status. Possible dietary factors that enhance or inhibit iron absorption can be evaluated from the dietary assessment. Other micronutrient deficiencies including iodine could have also impacted on the neonatal outcomes[37,38]. Therefore, these need to be investigated in detail in future research studies to ameliorate the effect of such confounders.

In conclusion, despite a decrease in serum ferritin concentration from 2nd trimester to 3rd trimester of pregnancy, pregnant women in our study were still categorised as iron sufficient as assessed by serum ferritin concentration. Given that iron deficiency is commonly reported among women of childbearing age and pregnant women, our study would like to emphasise the importance of early screening tests for iron status in antenatal care. Moreover, low iron status, particularly in 3rd trimester of pregnancy can cause some adverse neurodevelopmental outcomes in neonates. Future studies should investigate the sensitivity of different biomarkers for detecting maternal iron deficiency. The findings of this study can be used to inform the policy makers to formulate strategies to improve the maternal iron status, especially now the introduction of three-child policy in China.

Data availability

Data available on request from the corresponding authors (Hangzhou1988@hotmail.com and luyiming8686@163.com).

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Author contributions

HZ and YL were listed as the joint-first authors. HZ, JL, YL, BP, QZ, MC and ZFM contributed to the study conception and design. Data collection and analysis were performed by all authors. The first draft of the manuscript was written by HZ and ZFM, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflict of interest

The authors have no relevant conflict of interest to disclose.

Additional information

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