Original Article

Moderate NaFeEDTA and ferrous sulfate supplementation can improve both hematologic status and oxidative stress in anemic pregnant women

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Iron is important general well being, to prevent or treat anemia, and is a cofactor of many enzymes in the anti-oxidant process. Effect of sodium iron ethylenediaminetetraacetate (NaFeEDTA) and ferrous sulfate on iron bio-availability and oxidative stress in anemic pregnant women was evaluated. A 2-month randomized controlled trial was conducted on 153 anemic pregnant women, with 80≤ Hb <110g/L. They were randomly allocated to three groups: group C (n=51) was the placebo control group, group I (n=51) was supplemented daily with 60 mg iron as ferrous sulfate, and group IE (n=51) with 60 mg iron as NaFeEDTA. Blood samples were collected before and at the end of the intervention for measurements of hematological indices and oxidative stress parameters. Considerable increases of hematologic indicators were observed: 20.5 and 21.8 g/L for Hb (both *p* values <0.001); 4.81 and 7.19 μmol/L for plasma iron (both *p* values <0.001), 2.63 and 8.99 μg /L for ferritin (both *p* values <0.05) in I and IE groups, respectively, compared with the control group. Glutathione peroxidase (GSH-Px) activities increased by 32.6 and 75.3 IU/ml, and malondialdehyde (MDA) levels decreased by 0.70 and 1.12 μmol/L in I and IE groups, compared withthe C group (*p* values <0.05). Moreover, differences of plasma iron, ferritin and GSH-Px activity were 2.38 μmol/L, 6.36 μg /L and 42.7 IU/ml were also significantly greater in the IE group than in the I group. Moderate iron supplementation may be beneficial to improving iron deficiency and oxidative stress, and NaFeEDTA is better than ferrous sulfate.

Key Words: anemia, pregnant women, NaFeEDTA, ferrous sulfate, oxidative stress

INTRODUCTION

Iron deficiency is the most common and widespread nutritional deficiency in the world.[1] Prevalence of anemia is still high in rural areas in China.[2] The main causative factors are: poor iron content, low bioavailability of iron, or both of the largely vegetable-based diets that are typically consumed in many low-income countries.[3,4] Therefore, administration of iron supplements may be indicated if iron stores are inappropriately low at the start of pregnancy or impairment of the expected increase in hemoglobin mass in the mother is to be avoided.[5]

Ferrous iron, such as ferrous sulfate ($FeSO_4$) and sodium iron ethylenediamine- tetraacetate (NaFeEDTA) as two forms of iron supplements, is mostly used for correction of iron deficiency. $FeSO_4$, such as inorganic iron has been used to cure anemia since 1831. Its absorptivity is good but it is irritating to the stomach, causing gastrointestinal side effects, such as upper abdominal discomfort, nausea, and constipation.[6,7] NaFeEDTA is an iron chelate that has been used successfully as a dietary fortifier in several trials in the developing world,[8-10] as in this form, the iron is protected from inhibitors of iron absorption.

It has a bioavailability 2-4 times that of ferrous sulfate, especially in meals with high phytate content.[11] Therefore, is expected to effectively improve both of iron deficiency and gastrointestinal side effects in anemic pregnant women.

Pregnancy is a condition exhibiting increased susceptibility to oxidative stress, with both mothers and babies being exposed to oxidative stress during and after delivery.[12] Oxidative stress and damage have also been found in iron deficiency; however, increased malondialdehyde MDA levels in the maternal plasma and the placenta in the iron-supplemented group suggests that iron supplementation may contribute to increased oxidative stress in women taking iron supplements during pregnancy.[13]

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Manuscript received 19 February 2011. Initial review completed 20 June 2011. Revision accepted 30 July 2011.

Thus, pregnant women have a higher iron requirement, pregnancy or iron deficiency is a condition exhibiting increased susceptibility to oxidative stress and iron might play a role in generating harmful oxygen species. Therefore, the objective was to investigate the effect of iron supplements on hematological status and indicators of antioxidant status such as superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and malondialdehyde (MDA) levels in anemic pregnant women during the second and third trimester of pregnancy. It was hypothesized that NaFeEDTA would be better than ferrous sulfate at improving iron status and reducing oxidative stress

MATERIALS AND METHODS

Subjects

The study was a 2-month double-blind randomized trial. Participants were recruited between June 2003 and December 2005 from the communities of Shen county, Shandong province, China. At the start, pregnant women, 12 to 24-wk gestation, age range 20-30 years, were examined for eligibility. Finally, 153 anemic pregnant women with 80≤ Hb <110 g/L, no dietary supplements use during the previous 2 months and no abnormal pregnancy response, were allocated to the three groups in the order of enrollment. Group C (n=51) was the placebo control group, group I (n=51) was supplemented daily with 60 mg iron as ferrous sulfate, group IE (n=51) with 60 mg iron as NaFeEDTA. The capsules were labeled in red, yellow and blue color and manufactured by Hurun's company (a Chinese food-additive company, Beijing). Trial participants and the research team were unaware of the treatment assignment. The trial was unblinded after analysis of the primary outcomes.

After ascertainment of eligibility, consenting women were enrolled in the study, had a baseline interview and started with their allocated supplements to be taken daily for a period of two months. Women were visited at home once each week by the village nurse to replenish supplements and to monitor compliance by counting and recording the number of supplements that were taken.

The study was approved by the ethical review committees of the Medical College of Qingdao University. Written consent was given by each subject at the start of the trial. The subjects in the placebo group in our study have been given iron supplementation with NaFeEDTA or foods rich in iron, such as the hemachrome-iron from animal foodstuff, such as meat, fish and sea foods, immediately after the trial.

Sample collection and laboratory analyses

Before and at the end of the intervention, overnight fasting (>12 h) blood samples (about 5mL) were collected from subjects by venipuncture into heparinized tubes, between 6 and 8 o'clock in the morning; moreover, daily sample collection was evenly distributed over each of the groups. Hemoglobin concentrations were measured in heparinized blood. Plasma was separated from the remainder of the blood by centrifugation at 2000×g for 15 min at 4°C. The samples were transported on dry-ice and stored frozen at –80 °C until analysis for measurements of hematological indices and oxidative stress parameters. The baseline and final samples were analyzed in duplicate during the same analytic run.

Hemoglobin concentration was measured by the cyanomethemoglobin method by using HemoCue for confirmation. A cut-off value for anemia was Hb <110g/L. Measurements of serum ferritin were performed by radioimmunoassay.[14] Plasma iron concentrations were analyzed by atomic absorption spectrometry on an Analyst 3100 Analyzer (Perkin Elmer Life Sciences, Wellesley, MA). The soluble transferrin receptor (sTfR) assay was performed using a commercial kit (R&D Systems, Minneapolis, MN). According to the instruction of the kit, the central 95th percentile of the reference distribution of sTfR concentration is 4.0 to 9.1 mg/L. The cut-off value of iron deficiency was >9.1 mg/L. All sTfR assays were performed in duplicate. Total iron-binding capacity (TIBC) was determined by a turbidimetric method. A standard curve for each analyte was constructed from authentic standards. Standard concentrations were calculated on the basis of their known extinction coefficients.

The activities of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) were determined in plasma as U/ml and IU/ml, respectively.[15] One unit of SOD activ-

Table 1. Characteristics of subjects at baseline

Indicator[1]	All baseline		C[2]		I[2]		IE[2]		*p*-value[3]
	mean	SD	mean	SD	mean	SD	mean	SD	
n	153		51		51		51		
Age, years	28.1	3.6	27.6	3.3	28.4	3.5	28.4	3.6	0.394
Gravidity	1.33	0.47	1.29	0.46	1.37	0.49	1.33	0.48	0.707
Gestational stage, wk	21.4	4.69	21.2	4.75	21.5	4.48	21.5	4.92	0.936
Hb, g/L	100	7.9	102	9.0	99.9	6.1	99.8	8.0	0.164
sTfR, mg/L	10.5	2.2	10.2	2.8	11.0	1.78	10.5	2.20	0.132
PI, μmol/L	12.2	2.93	12.7	3.13	11.9	2.00	11.9	3.43	0.275
Ferritin, μg/L	12.7	4.78	13.1	5.28	13.1	2.58	11.8	5.83	0.313
TIBC, %	80.7	11.4	78.7	10.5	81.8	10.6	81.7	11.4	0.312
MDA, μmol/L	5.21	1.53	5.11	1.25	5.54	1.88	4.97	1.34	0.137
SOD, U/ml	76.9	28.7	73.5	34.1	75.9	23.4	81.2	27.5	0.378
GSH-Px, IU/ml	117	26.5	111	26.3	119	26.7	121	25.8	0.131

[1]Indicators and abbreviations: Hb, hemoglobin concentration; PI, plasma iron; sTfR, soluble transferrin receptor; TIBC, total iron-binding capacity; MDA,Malondialdehyde; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase. [2]group C as placebo, group I was supplemented with 60 mg iron as ferrous sulfate; group IE with 60 mg iron as NaFeEDTA; [3]*p*-value of the difference across treatment groups tested by one way ANOVA.

ity was defined as the amount of protein causing 50% inhibition of the nitroblue tetrazolium salt reduction rate. The MDA concentration was determined by using the thiobarbituric acid reaction. The MDA, an end product of fatty acid peroxidation, reacts with thiobarbituric acid to form a colored complex that has maximum absorbance at 532 nm. MDA concentrations were calculated by comparing the absorbance values of the samples with those of standard MDA solutions. Results were expressed as μmol/L blood.[16] All oxidative indicators were calculated from their standard curves.

Statistical analysis

Continuous data are presented as mean±SD or mean± SEM. Baseline variables were compared across three groups using a general linear model ANOVA. Mean changes over the intervention period and differences between groups and 95% confidence intervals (CI) were estimated for hematologic indicators and oxidative indicators, and tested with Student *t*-tests. The SPSS 18.0 package was used for all analyses. A p-value < 0.05 was considered as significant for all tests.

RESULTS

In the intervention study, complete data were available from 147 women, which is 96.1% of the original number of 153 pregnant women. Six women did not complete the trial due to the following reasons: 4 moved to other villages; 2 stopped taking supplements during the trial. Moreover, compliance was excellent, because study subjects were motivated by the offer of free medical care and all women were visited weekly by village nurses, who counted leftover capsules, provided new supplies, and gave support in case of any problems or questions related to the study. At the end of the trial, there were no substantial differences between the groups in any of the baseline characteristics (Figure 1). The groups did not differ in age, gestational stage, gravidity, hematological status, levels of MDA, SOD and GSH-Px at baseline (p>0.05) (Table 1).

After the 2-month supplementation, significant changes in the placebo group were -3.64 g/L in Hb concentration, 0.87 mg/L in sTfR, -1.23 μmol/L in plasma iron and -1.59 μg /L in ferritin, compared with baselines (all p-values <0.05). Considerable increases in hematologic indicators were: 20.5 and 21.8 g/L for Hb (all p-values <0.001); 4.8 and 7.2 μmol/L for plasma iron (both p-values <0.001), 2.6 and 9.0 μg /L for ferritin (both p-values <0.05); and decreases in TIBC: 31.4% and 26.6% (both values *p-values* <0.001) in I and IE groups, respectively, compared with the control group (Table 2). The differences of plasma iron and ferritin were 2.38 μmol/L and 6.37 μg /L, also significantly greater in the IE group than in the I group (both p-values <0.001).

The changes in oxidative stress parameters are presented in Table 3. Compared with C, increases of GSH-Px activities were 32.6 IU/ml and 75.3 IU/ml in I and IE groups (both p-values <0.05), respectively; the levels of MDA decreased by 0.70 and 1.11 μmol/L in the two treated groups (both p-values <0.05), respectively. Moreover, the increase of GSH-Px activity was 42.7 IU/ml greater in IE group compared with I group (p <0.001).

DISCUSSION

After 2 months trial, both NaFeEDTA and ferrous sulfate supplementation in anemic pregnant women did not only significantly improve hematologic indicators, but also reduced oxidative stress, as shown by increased GSH-Px activities and decreased levels of MDA. An additional effect was found in iron status and GSH-Px activity for NaFeEDTA compared to ferrous sulfate supplementation.

Normal human pregnancy is considered to be a state of enhanced oxidative stress, which may play an important role in embryo development, implantation, placental development and function, foetal development, and labour in pregnancy.[17] However, pathologic pregnancies including gestational diabetes mellitus (GDM), obesity and

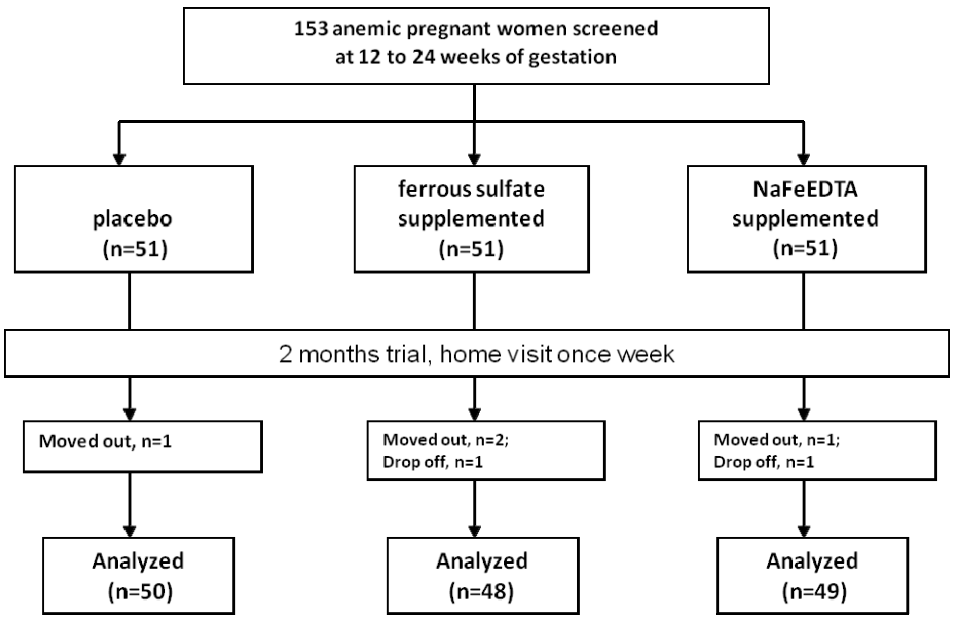

Figure 1. The trial profile. After ascertainment of eligibility, 153 consenting pregnant women were enrolled in the study. After the 2 month trial, complete data were available on 147. There were no substantial differences between the groups in any of the baseline characteristics.

Table 2. Changes and differences in indicators for hematological status in three groups

Indicator[1]	Group[2]	n	Changes[3]			Difference[4]			Difference[5]		
			mean	95%CI	*p*-value	mean	95%CI	*p*-value	mean	95%CI	*p*-value
Hb, g/L	C	50	-3.6	-6.6, -0.4	0.026	--	--	--	--	--	--
	I	48	19.4	16.3, 22.8	<0.001	20.5	17.3, 23.8	<0.001	--	--	--
	IE	49	20.8	17.6, 24.1	<0.001	21.8	18.9, 25.1	<0.001	1.30	-1.98, 4.58	0.435
sTfR, mg/L	C	50	0.87	0.14, 1.60	0.019	--	--	--	--	--	--
	I	48	-4.37	-5.10, -3.36	<0.001	-5.20	-5.94, -4.46	<0.001	--	--	--
	IE	49	-5.61	-6.35, -4.87	<0.001	-5.70	-6.44, -4.95	<0.001	0.49	-1.24, 0.26	0.196
PI, μmol/L	C	50	-1.23	-2.12, -0.34	0.007	--	--	--	--	--	--
	I	48	4.40	3.50, 5.30	<0.001	4.81	3.91, 5.72	<0.001	--	--	--
	IE	49	6.75	5.86,7.65	<0.001	7.19	6.29, 8.09	<0.001	2.38	1.47, 3.29	<0.001
Ferritin, μg/L	C	50	-1.59	-3.15, -0.02	0.047	--	--	--	--	--	--
	I	48	0.98	-0.61, 2.56	0.226	2.63	1.04, 4.22	0.001	--	--	--
	IE	49	8.62	7.05, 10.2	<0.001	8.99	7.41, 10.6	<0.001	6.36	4.76, 7.96	<0.001
TIBC, %	C	50	3.11	-0.31, 6.52	0.075	--	--	--	--	--	--
	I	48	-31.3	-34.8, -27.9	<0.001	-31.4	-34.8, -27.9	<0.001	--	--	--
	IE	49	-26.4	-29.8, -23.0	<0.001	-26.6	-30.0, -23.1	<0.001	4.80	1.13, 8.29	0.007

[1]Indicators and abbreviations: Hb, Hemoglobin concentration; PI, plasma iron; sTfR, soluble transferrin receptor; TIBC, total iron-binding capacity.[2]group C as placebo, group I supplemented with 60 mg iron as ferrous sulfate; group IE with 60 mg iron as NaFeEDTA; [3]Changes: value at end of trial subtracted from baseline value within group; [4]Differences: changes in the group I (or IE)- changes in the control group, respectively; [5]Differences: changes in the group IE- changes in the group I.

Table 3. Changes and differences of oxidative stress in MDA, GSH-Px and SOD in three groups

Indicator[1]	Group[2]	n	Changes[3]			Difference[4]			Difference[5]		
			mean	95%CI	*p* value	mean	95%CI	*p* value	mean	95%CI	*p* value
MDA, μmol/L	C	50	0.17	-0.33, 0.66	0.502	--	--	--	--	--	--
	I	48	-1.11	-1.61, -0.61	<0.001	-0.70	-1.20, -0.20	0.006	--	--	--
	IE	49	-0.91	-1.40, -0.41	<0.001	-1.12	-1.61, -0.62	<0.001	-0.41	-0.92, 0.09	0.108
SOD, U/ml	C	50	1.19	-9.87, 12.3	0.832	--	--	--	--	--	--
	I	48	0.22	-11.0, 11.4	0.696	1.47	-9.76, 12.7	0.797	--	--	--
	IE	49	-11.7	-22.8, -0. 6	0.039	-5.10	-16.3, 6.07	0.370	-6.57	-17.9, 4.7	0.253
GSH-Px, IU/ml	C	50	10.6	-4.23, 25.5	0.160	--	--	--	--	--	--
	I	48	29.5	14.2, 44.3	<0.001	32.6	17.5, 47.7	<0.001	--	--	--
	IE	49	66.2	51.3, 81.1	<0.001	75.3	60.3, 90.3	<0.001	42.7	27.5, 57.9	<0.001

[1]Indicators and abbreviations: MDA, malondialdehyde; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase. [2]group C as placebo, group I supplemented with 60 mg iron as ferrous sulfate; group IE with 60 mg iron as NaFeEDTA; [3]Changes: value at end of trial subtracted from baseline value within group; [4]Differences: changes in the group I (or IE)- changes in the control group, respectively; [5]Differences: changes in the group IE- changes in the group I.

hypertensive disorders are associated with a heightened level of oxidative stress.[18-20] Maternal undernutrition, particularly at a time that includes pregnancy, results in reduced offspring ovarian follicle numbers and may be mediated by increased ovarian oxidative stress coupled with a decreased ability to repair the resultant oxidative damage.[21] Untreated iron deficiency is deleterious, while iron overload could promote the generation of free radicals and result in cellular damage[22]. It is, therefore, important to maintain optimal iron intake.[23] Low doses of oral ferrous iron (36 mg/d) did not unfavorably change the physiological pattern of parameters of oxidation.[24] Daily supplementation of 100 mg iron as ferrous sulfate during the second half of pregnancy was recommended to address the corresponding iron requirements,[25] and risks associated with oxidative stress were not observed in women supplemented with 120 mg iron once or twice per week.[26] Suggested guidelines are 80-100 mg ferrous iron daily, for which there are no documented side effects[5]. In our study, the moderate supplementation with 60mg/d iron has been beneficial to improving hematological status and oxidative stress parameters. We found that MDA levels, a marker of lipid peroxidation, were significantly decreased and GSH-Px activity increased in two supplemented groups, which indicates that the moderate iron supplementation improved oxidative status without increased deleterious effects.

Unfortunately, the hematologic status of pregnant women in the second or third trimester of pregnancy in the placebo group deteriorated after the trial, and the changes of Hb concentration, ferritin and plasma iron levels decreased, which might be contributing to blood volume expansion and iron deficiency. During the period of pregnancy, plasma volume expands by 25% to 80% of pre-pregnancy volumes.[27] Pregnant women have an increased demand for iron to expand about 30% of their erythrocyte mass and generate the iron supply to the growing fetus[28], which results in a decrease of hematocrit of about 3% to 5% between gestational weeks 20 and 30.[29] Therefore, 80-100 mg ferrous iron/day for women with iron deficiency (ID) and iron deficiency anemia (IDA) should be recommended.[30]

With respect to changes of iron supplementation and oxidative stress parameters in this study, subjects also had

significantly higher glutathione peroxidase activity and low level of plasma MDA after iron supplementation. This finding is in accordance with previously reported data in human and animal models.[31,32] Ferrous iron is the form that is mostly used for correction of iron deficiency, and a central pro-oxidant that propagates free radical reactions through Fenton chemistry both locally (in the gastrointestinal tract) and systemically. An excess of pro-oxidants over antioxidants results in oxidative stress, but there was no increase in the markers of oxidation or inflammation studied. Moreover, we could not find any indication of an increase of oxidative stress after iron supplementation. On the contrary, the moderate dose of iron may be beneficial both in improving anemia and decreasing the status of oxidative stress during pregnancy.

NaFeEDTA might be a better form of iron supplements than electrolytic iron.[33] Iron absorption from NaFeEDTA might be two to three times higher than from electrolytic iron.[34] NaFeEDTA increased both Hb concentration and serum ferritin concentration substantially in iron deficient populations[35]. At least 10 mg/d iron as NaFeEDTA would be necessary to prevent iron deficiency anemia even in populations relying for their subsistence on vegetable food only; although those suffering from severe anemia would require more than 10 mg/d.[36]

Several studies showed that NaFeEDTA is more suitable than electrolytic iron in children,[10,37] but few reports were related to anemic pregnant women. The study showed that iron deficiency among pregnant women untreated in the middle trimester of pregnancy might deteriorate in the third trimester in terms of both hematologic status and oxidative stress; and moderate iron supplementation has been beneficial in improving iron deficiency and oxidative stress, and NaFeEDTA is better than ferrous sulfate. Thus, based on the results from this study, we suggest that iron supplementation with NaFeEDTA should be recommended for anemic pregnant women. Surprisingly, almost none of the subjects with poor nutritional status took dietary supplements, including iron. Our study has important public health implications. It underlines the need for a comprehensive nutritional policy for this target population. Besides improving their diet, NaFeEDTA supplementation may be worthwhile for pregnant women in rural China.

ACKNOWLEDGMENTS

This work was supported by a grant from Danone Nutrition Institute China.

AUTHOR DISCLOSURES

Han XX, Sun YY, Ma AG, Yang F, Zhang FZ, Jiang DC and Li Y, no conflicts of interest.

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Original Article

Moderate NaFeEDTA and ferrous sulfate supplementation can improve both hematologic status and oxidative stress in anemic pregnant women

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EDTA 铁补充能有效地改善孕妇贫血及氧化应激水平

背景与目的：铁不仅是重要的营养素可预防贫血，而且作为辅酶可参与机体抗氧化反应。本研究拟评价 EDTA 钠铁盐 (NaFeEDTA) 和硫酸亚铁盐 ($FeSO_4$) 补充对贫血孕妇铁的生物利用率和氧化应激水平的影响。方法：采用随机对照研究方法，选择 153 名贫血孕妇 (血红蛋白在 80g/L~110g/L 之间)，随机分为 3 个组，分别是对照组 C 给予安慰剂；$FeSO_4$ 组 I，每天补充含 60 mg 铁的 $FeSO_4$；NaFeEDTA 组 IE，每天给予含 60 mg 铁的 NaFeEDTA，补充干预 2 个月。结果：干预结束后，与对照组相比，$FeSO_4$ 和 NaFeEDTA 补充组血红蛋白水平分别升高了 20.5 g/L and 21.8 g/L (p 值均<0.05)，血浆铁水平升高了 4.81 μmol/L 和 7.19 μmol/L (p 值均<0.05)，铁蛋白水平上升了 2.63 μg/L 和 8.99 μg/L (p 值均<0.05)，抗氧化酶谷胱甘肽过氧化物酶 (GSH-px) 活性上升了 32.6 IU/ml and 75.3 IU/ml (p 值均<0.05)，脂质过氧化产物 (MDA) 水平下降了 0.70 μmol/L 和 1.12 μmol/L (p 值均<0.05)。进一步分析发现，NaFeEDTA 补充组血浆铁、铁蛋白水平、GSH-px 活性比 $FeSO_4$ 组明显升高，分别上升了 2.38 μmol/L、6.36 μg /L 及 42.7 IU/ml (p 值均<0.05)。结论：孕中期贫血妇女如不及时补铁，在孕晚期可使机体贫血及缺铁情况加重，机体氧化应激水平进一步升高；而及时补铁可明显改善孕妇贫血状况，NaFeEDTA 补充效果明显好于 $FeSO_4$ 补充效果。

关键字：贫血、孕妇、NaFeEDTA、硫酸亚铁、氧化应激