

An Overlooked Side Effect of Iron Treatment: Changes in Menstruation

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ABSTRACT

AIM: Iron deficiency is one of the most common nutritional problems of the human race. Iron has been used to treat anemia for more than 300 years. It is known very well that oral iron treatment have some side effects. Contrary to well defined side effects, we have observed some menstrual changes in some patients receiving oral iron treatment. Therefore, we aimed to evaluate these findings and discuss the underlying potential mechanisms.

METHOD: One hundred twenty eight nonpregnant female patients who were diagnosed with iron deficiency anemia were enrolled in the study. Menstrual status at the time of diagnosis and menstrual changes 2 months after the iron treatment were noted for all patients.

RESULTS: We detected menstrual changes in half of the iron receiving patients.

CONCLUSION: This is the first report of a correlation between iron treatment and menstrual changes, and we consider that this side effect is overlooked by the clinicians. Although its mechanisms

are unclear, many factors are considered to affect this side effect and we suggest that the possible underlying mechanisms should be investigated.

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Key words: Iron, anemia, menstruation

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INTRODUCTION

Iron deficiency is one of the most common nutritional problems of the human race^[1]. It can cause reduced work capacity in adults and impact motor and mental development in children and adolescent^[2]. More than 1.6 billion people, almost a quarter of the world's population, are anemic^[3]. The World Health Organization (WHO) estimates that worldwide, 42% of pregnant women, 30% of nonpregnant women (aged 15 to 50 years), 47% of preschool children (aged 0 to 5 years), and 12.7% of men older than 15 years are anemic^[3].

Iron has been used to treat anemia for more than 300 years^[4]. Oral iron replacement therapy with gradual replenishment of iron stores and restoration of hemoglobin is the preferred treatment^[5]. It is known very well that oral iron treatment have some side effects. Major side effects of oral treatment include epigastric discomfort, nausea, vomiting, abdominal cramps, diarrhea, and constipation^[6,7].

In addition to well defined side effects, we have observed some menstrual changes in some of the patients receiving oral iron treatment. Therefore, we aimed to evaluate these findings and discuss the possible underlying mechanisms.

Table 1 Laboratory data of the patients on admission and after iron treatment.

| | All Patients (n=128) | | Patients with no menstrual changes (n=64) | | Patients with menstrual changes (n=64) | |
|--|----------------------|------------------|---|------------------|--|------------------|
| | Baseline | After Treatment | Baseline | After Treatment | Baseline | After Treatment |
| WBC ($\times 10^3 / \mu\text{L}$) | 6.5 \pm 1.8 | 6.7 \pm 1.9 | 6.6 \pm 2.0 | 6.6 \pm 1.7 | 6.4 \pm 1.7 | 6.8 \pm 2.0 |
| RBC ($\times 10^{12} / \text{L}$) | 4.41 \pm 0.38 | 4.80 \pm 0.39 | 4.41 \pm 0.39 | 4.78 \pm 0.38 | 4.41 \pm 0.38 | 4.81 \pm 0.41 |
| Hb (g/dL) | 9.7 \pm 1.4 | 12.5 \pm 1.0 | 9.9 \pm 1.4 | 12.5 \pm 1.0 | 6.5 \pm 1.5 | 12.4 \pm 1.0 |
| Hct (%) | 31.1 \pm 3.9 | 38.0 \pm 2.8 | 31.4 \pm 4.3 | 37.9 \pm 2.8 | 30.7 \pm 3.6 | 38.1 \pm 2.9 |
| MCV (fL) | 70.3 \pm 8.0 | 80.4 \pm 5.2 | 71.5 \pm 7.7 | 80.8 \pm 4.9 | 69.8 \pm 8.2 | 80.0 \pm 5.5 |
| RDW (%) | 18.1 \pm 3.4 | 21.7 \pm 6.1 | 18.0 \pm 3.1 | 21.6 \pm 6.0 | 18.2 \pm 3.6 | 22.0 \pm 6.2 |
| PLT ($\times 10^9 / \text{L}$) | 307 \pm 85 | 276 \pm 62 | 292 \pm 74 | 272 \pm 60 | 322 \pm 92 | 281 \pm 64 |
| Serum Iron ($\mu\text{g} / \text{dL}$) | 23.7 \pm 9.2 | 60.8 \pm 24.7 | 24.7 \pm 8.0 | 62.2 \pm 25.0 | 22.8 \pm 10.3 | 59.4 \pm 24.6 |
| Serum UIBC ($\mu\text{g} / \text{dL}$) | 418.5 \pm 53.9 | 323.7 \pm 49.4 | 412.3 \pm 54.7 | 324.3 \pm 43.6 | 424.7 \pm 52.7 | 323.2 \pm 54.8 |
| Serum Ferritin (ng/mL) | 5.4 \pm 4.7 | 24.9 \pm 15.9 | 5.8 \pm 5.4 | 24.2 \pm 14.6 | 5.1 \pm 3.9 | 25.6 \pm 17.2 |
| TSI (%) | 5.5 \pm 2.4 | 16.9 \pm 6.9 | 5.8 \pm 2.1 | 16.3 \pm 6.8 | 5.2 \pm 2.6 | 15.9 \pm 7.1 |

METHOD

Study Group

This was a prospective multi-centric study. The patients were selected independently from the etiology. One hundred twenty eight nonpregnant female patients (aged 18-50 years) who were diagnosed with iron deficiency anemia were enrolled in the study. The subjects who had severe endocrinological, psychiatric disorders, oncological diseases, significantly irregular cycles or receiving medications which could affect menstrual cycles were excluded from the study.

Laboratory Studies

Complete blood count, serum iron, serum unsaturated iron binding capacity and serum ferritin levels were noted at the time of diagnosis and two months after iron therapy. Transferrin saturation index (TSI) was calculated as the ratio of serum iron to TIBC \times 100. Iron deficiency anemia was defined according to World Health Organisation criteria as hemoglobin level <12 gr/dL, serum ferritin level <15 ng/mL and/or transferrin saturation $<16\%$.

Iron Treatments

For oral medication, 80-160 mg elemental iron equivalent to 270-540 mg iron II sulfate/day was used for two months.

Assessment of Menstrual Status

At the end of two months of iron therapy, the patients were questioned about the menstrual changes which has occurred within the recent 2 months beginning from iron therapy.

Statistical Analysis

Patients characteristics were examined using descriptive statistics. Continuous variables were given as mean \pm standard deviation (SD), and categorical variables were defined as percentage. Chi-squared test and T-test were used to compare proportions and means for categorical and continuous variables, respectively. Bivariate correlation analyses were performed to examine the association between menstrual changes and the other parameters. The variables which have significant p values ($p < 0.05$) and marginal insignificant p values ($p < 0.1$) in univariate analysis were included in the multivariate analysis. All test significance were two-tailed. The SPSS statistical software (SPSS 17.0 for Windows, Inc., Chicago, IL, USA) was used for all statistical calculations.

RESULTS

The study included 128 nonpregnant female patients with mean age of 34.6 ± 10.0 years. While menstrual changes were observed in 50% of the patients, no changes occurred in the remaining 50%. Of the

patients with menstrual changes, 24 (18.8%) had increased menstrual bleeding, 25 (19.5%) had decreased menstrual bleeding, 10 (7.8%) had early menstrual bleeding, 5 (3.9%) had delayed menstrual bleeding. Laboratory data of the patients on admission and after iron treatment are shown Table 1.

A statistically significant difference was not found between groups with regard to WBC, RBC, hemoglobin, hematocrit, MCV, RDW, serum iron, UIBC, serum ferritin, TSI values on admission and after treatment ($p > 0.05$), a significant difference was found only between the platelet counts on admission ($p = 0.39$). A significant correlation could not be detected between menstrual changes and any variables in correlation analysis ($p > 0.05$).

DISCUSSION

In the present study, we found that menstrual changes occurred in half of the patients during iron treatment and these changes did not correlate with any significant parameters. It is not easy to explain the mechanism of this side effect due to the absence of literature data. However, we consider that various factors (e.g., endometrial proliferation affecting factors, directly/indirectly effects of iron, vascular effects, estrogens, or hematologic effects) may lead to this side effect.

Iron is an absolute requirement for proliferation, as iron-containing proteins catalyse key reactions involved in oxygen sensing, energy metabolism, respiration, folate metabolism and DNA synthesis^[8]. It has been shown that subunit R2 of the ribonucleotide reductase gene contains iron-specific regulatory elements and is up-regulated by blood flow^[8]. In fact, deprived of iron, cells are unable to proceed from the G1 to S phase of the cell cycle^[8]. Based on this data, it is likely that iron treatment can affect menstruation via increased cell proliferation in the endometrium.

Vascularization is a normal physiological process during folliculogenesis, the development of the endometrium, implantation, placentation and in embryonic development^[9]. Various substances have been cited as possible factors in vascularization: growth factors, cytokines, adhesion molecules and extracellular matrices^[9]. With regard to growth factors and cytokines, platelet-derived growth factor, vascular endothelial growth factor (VEGF), tumor growth factor- β and tumor necrosis factor (TNF)- α have been suggested to have a role in vascularization^[9]. It was shown that iron deficiency increases hypoxia-inducible factor-1 α (HIF-1 α), VEGF, and angiogenesis^[10,11]. Xie *et al*^[12] also reported that labile iron pool (iron in transit) is common denominator of ferritin both in enhancement of cell death by basal steady-state H-ferritin and in protection against cell death by induced H-ferritin, thereby acting as a key determinant of TNF-induced cell death. It is seen that there were various complex relationships between iron and growth factors. Based on these

relationships, we may conclude that vascularization of endometrium may be affected during iron therapy.

Vasoconstriction of endometrial spiral arteries is a significant factor in menstruation, and various factors affect vasoconstriction or vasodilatation of arteries^[9]. There is increasing evidence that a majority of prostoglandins cause significant vasodilatation^[9]. The cellular level of heme is regulated by the rate of its synthesis and degradation^[13]. Heme degradation occurs almost exclusively by oxidative cleavage of the a-meso carbon bridge of heme, eventually leading to the formation of equimolar amounts of biliverdin, iron, and carbon monoxide^[13]. The heme oxygenase (HO) system controls the rate-limiting step in heme degradation^[13]. The authors demonstrated that the increase in HO activity was associated with a subsequent decrease in cyclooxygenase (COX) activity, which returned to normal levels following normalization of HO activity^[13]. The addition of heme resulted in an increase in COX activity with an increase in prostoglandin (PG) E2 and 6-keto-PGF1a levels^[13]. It was interpreted that the heme-HO system can function as cellular regulator of the expression of vascular COX, thus influencing the generation of prostanoids, PGE2 and PGI2, known to play role in vascular homeostasis^[13]. Mancuso *et al*^[14] also reported that HO regulates COX activity by reducing the intracellular heme content or by generating CO, which stimulates PGE2 release. According to these data, we may state that there is a relationship between iron metabolism and COX systems.

Within the vascular compartment, iron is primarily contained in hemoglobin and storage forms such ferritin and hemosiderin^[15]. Less commonly considered is iron's vital role in enzymes such as the respiratory cytochromes, cytochrome P-450, nitric oxide (NO) synthases^[15]. Endothelial nitric oxide synthase (eNOS) controls blood pressure, blood flow and oxygen delivery through its effect on vascular smooth muscle tone^[16]. Iron deficiency anemia can increase NO production in adolescents and greatly reduce its removal by virtue of decreased hemoglobin^[15]. In particular, plasma ferritin concentrations relate directly to NO mediated vasodilatation and endothelial function^[15]. Another finding is that NO, originally identified in vascular endothelial cells, is present in glandular epithelial cells in the endometrium^[9]. All these data indicated that iron affects various levels of NO production and blood flow in endometrium.

There was also a relationship between estrogen and iron^[10,17-19]. This interaction largely consists of estrogen effects on menstrual blood flow, a major source of iron loss in premenopausal women^[17]. However, Xi Huang *et al*^[17] described a direct mechanism of interaction between estrogens and hepcidin. Specifically, it is observed that estrogen can decrease the expression of hepcidin mRNA by an estrogen response element half-site upstream in hepcidin promoter^[17]. Ikeda *et al*^[18] reported that estrogen played a role in hepcidin expression in G-coupled protein 30 (GPR30)-bone morphologic protein 6 (BMP6)-dependent manner in vitro. In conclusion, many studies indicated that estrogen affects iron metabolism via hepcidin, but it is not known whether estrogen is affected by iron directly or hepcidin-mediated. According to the knowledge that various hormonal/metabolic axes have feedback mechanisms in the organism, if there is an estrogen-hepcidin-iron axis, it is likely that there is also an iron-hepcidin-estrogen axis. However we consider that it should be examined with further studies. Additionally, the relationships between with iron and platelet function were shown in many studies^[20,21]. Yildirim *et al*^[20] reported that platelet aggregation and adhesion have been delayed in children with iron deficiency anemia. Pratićo *et al*^[21] found that iron (Fe²⁺)

dose-dependently induced platelet aggregation, thromboxane B2 formation, and protein kinase C (PKC) translocation from the cytosol to the cell membrane. This study showed that iron can directly interact with human platelets, resulting in their activation^[21]. Its action is mediated by hydroxyl radical formation and involves PKC activity^[21].

According to our findings and literature data, it is very difficult to explain the menstrual changes occurring during iron treatment with a single mechanism. Because different menstrual changes were detected to occur. Therefore, we may consider that this side effect is affected by many factors. As discussed previously, iron can affect endometrial metabolism and cycles in various stages. But we do not have not sufficient data about the effects of iron treatment on stages of menstrual cycle, the predominant mechanisms effective at certain stages of menstrual cycle, and we cannot predict the side effects that will occur in certain patients.

CONCLUSION

This is the first report of a correlation between iron treatment and menstrual changes, and we consider that this side effect is overlooked by clinicians. Although its mechanisms are unclear, it is likely that many factors affect this side effect. We conclude that further prospective studies conducted with larger patient populations are required to investigate the underlying mechanisms of menstrual changes during iron treatment.

STUDY LIMITATIONS

Despite its contribution to the literature, our study has some limitations. Although this study was designed as a prospective study, we noticed that not recording the day of iron therapy commencement hindered us to make an analysis about whether it had an influence on the menstrual changes. Second, we could not follow up the patients for the future menstrual changes after completion of the iron treatment. Finally, we could not reveal the potential underlying mechanisms as our study was an observational study.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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