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Original Article

Efficacy and Safety of Feroxyl® in Pregnant Libyan Women From Second Trimester Onward: A Prospective Observational Study

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Abbreviations GI: Gastrointestinal; Hb: Hemoglobin; IDA: Iron Deficiency Anemia; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; MCV: Mean Corpuscular Volume

Abstract

Introduction: *Ferrous bis-glycinate is an oral iron preparation that shows great efficacy in increasing Hb and ferritin levels in pregnant women and children with iron deficiency anemia (IDA). It has been found to be more bioavailable and associated with fewer gastrointestinal side effects compared to iron salts.*

Objectives: *This study aims to investigate the effects of Feroxyl®, a combination of ferrous bis-glycinate and vitamins C, D, B9, and B12 on hemoglobin (Hb) and ferritin levels and other hematological outcomes such as mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and to report the occurrence of any side effects.*

Methods: *This prospective chart review was conducted on 50 pregnant women with moderate or mild IDA at gestational ages between 20 and 32 weeks. Clinical examination and blood tests for Hb, complete blood count, and serum iron indices were performed at baseline and 6-week follow-up visits.*

Results: *Supplementation with Feroxyl® demonstrated significant improvements in hematological parameters including Hb and serum ferritin levels, MCV, MCH, and MCHC, which increased significantly ($p<0.001$) compared to baseline. The study also highlighted the tolerability of Feroxyl®, showing that 70.7% of participants experienced no adverse events after 6 weeks of supplementation.*

Conclusions: *Feroxyl® supplementation for 6 weeks is both effective and well tolerated for the treatment of IDA in pregnant women, significantly improving Hb and serum ferritin levels and other blood parameters, with a low incidence of side effects.*

Introduction

Iron deficiency anemia (IDA) is a common global nutritional deficiency affecting half a billion women. This significant public health problem is particularly severe during pregnancy, affecting 37% of pregnant women worldwide and predisposing them to maternal mortality and morbidity [1,2]. IDA in pregnancy is diagnosed and classified based on hemoglobin (Hb) concentration: mild anemia with Hb levels between 10.0 and 10.9 g/dL, moderate anemia between 7.0 and 9.9 g/dL, and severe anemia when Hb levels are less than 7.0 g/dL, with slight variation depending on the trimester of pregnancy [1,3]. Serum ferritin levels are also used as a marker for IDA in pregnancy when levels fall below 20 - 30 g/L [4,5].

A common and effective approach to treating IDA in pregnancy is oral supplementation to replenish iron stores and normalize Hb levels. Ferrous salts, including ferrous sulfate, ferrous fumarate, ferrous gluconate, ferrous ascorbate, and ferrous glycine sulfate, are traditional forms of supplemental iron that require high doses of 150 to 300 mg for treatment due to their low bioavailability [6]. Ferrous iron preparations can also irritate the gastric mucosa and cause various adverse gastrointestinal (GI) side effects, including heartburn, nausea, constipation, diarrhea, and abdominal pain [7,8]. This poses a significant challenge to supplement adherence, potentially leading to reduced treatment efficacy.

Ferrous bis-glycinate, an oral iron formulation, is an amino acid iron chelate [9] that has been shown to be more bioavailable and associated with fewer GI side effects compared to iron salts [10–13]. This newer low-dose oral iron preparation (30-60 mg/day) has also shown great efficacy in increasing Hb and ferritin levels and mean corpuscular volume (MCV) in pregnant women and children [10–12,14–16]. While ferrous bis-glycinate has not yet been extensively studied as a combination therapy for the treatment of IDA, only one recent study has demonstrated the beneficial effects of its combination with folinic acid and multivitamins on hematological parameters in pregnant women with IDA [17]. The increases in Hb, MCV, mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration (MCHC), and ferritin levels suggest the potential benefits of combining ferrous bis-glycinate with additional vitamins for better management of IDA in pregnancy.

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As pregnant women already experience pregnancy-related symptoms such as nausea and heartburn, the provision of effective and well-tolerated oral iron supplements is crucial for the prevention and treatment of IDA in pregnancy. Since studies investigating the combination of ferrous bis-glycinate with other nutrients are limited, the primary objective of this study was to evaluate the effects of Feroxyl®, a combination of ferrous bis-glycinate and vitamins C, D, B9, and B12, on Hb and ferritin concentrations, and the secondary objective was to evaluate Feroxyl® GI adverse events in pregnant women with mild to moderate IDA.

Methods

Study design and settings

This study was designed as a prospective chart review study to evaluate the effects of Feroxyl®, a combination of ferrous bis-glycinate (27 mg) and vitamins C (75 µg), D (1000 IU), B9 (400 µg), and B12 (2.4 µg) on moderate or mild IDA in pregnant women. The supplementation regimen consisted of administering one capsule of Feroxyl® per day for women with Hg levels between 9.5 and 10.5 g/dL, and two capsules of Feroxyl® per day for those with Hg levels between 8 and 9.5 g/dL for 6 weeks.

Data were collected from the patients' medical records using an electronic case report form (e-CRF) at baseline and at 6-week follow-up at the Benghazi Medical Center, Benghazi, Libya, from 1st January to March 30, 2020.

Study participants

Pregnant women with mild (Hb level between 9.5 and 10.4 g/dL) or moderate (Hb level between 7.0 and 9.4 g/dL) IDA at 20 to 32 weeks' gestation were eligible for the study. Women with severe IDA (Hb level < 7.0 g/dL) or other types of anemia were excluded from the study.

At baseline, 50 participants were enrolled. At the 6-week follow-up, 41 participants were compliant with the supplementation protocol and completed the study. Nine women did not adhere to the protocol or had a termination of pregnancy and were excluded from the study.

Data collection and outcome measures

At the beginning of the study and at the first visit to the medical center, a detailed medical history of the participants was obtained. Clinical examination and blood tests for Hb, complete blood count, peripheral smear, total iron binding capacity, and serum iron indices were performed at the baseline and follow-up visits. The occurrence of side effects was also recorded at the second visit after the end of the supplementation period.

To evaluate the efficacy of Feroxyl® supplementation, the main study parameter was Hg levels measured before and after the supplementation period. Other hematological parameters including MCV, MCH, MCHC and serum ferritin were also assessed to provide a comprehensive evaluation of the hematological status of the participants before and after treatment. Another objective of the study was to collect information on the side effects of Feroxyl® in order to assess its safety and tolerability in pregnant women.

Ethics approval and consent to participate

At the first visit, information about the aim and the purpose of the study was provided and participants were requested to sign a consent form prior to their participation in the study. The Medical Affairs Department at the Benghazi Medical Center in Libya reviewed and ethically approved the study protocol.

Statistical analysis

Continuous variables, including Hg level, MCV, MCH, MCHC, and serum ferritin level, were summarized as mean and standard deviation and analyzed by paired samples t-test to determine the statistical significance of differences between the two visits. Age and adverse events, as categorical variables, were presented as frequencies and percentages. Statistical significance was set at a two-tailed p-value < 0.05. All statistical analyses were performed using Stata v17.0 software.

Results

Participants demographics

The study included 41 Libyan pregnant women with IDA. The age distribution of the study population is shown in Table 1. The mean age of the participants was 30.4 years, with a standard deviation of 5.4 years. The oldest participant was 40 years old, while the youngest was 21 years old.

Table 1. *Age distribution of Libyan pregnant women with iron deficiency anemia included in the study (n=41).*

Age group (years)	Frequency (n)	Percentage (%)
20 – 25	10	24.4
26 - 30	10	24.4
31- 35	18	43.9
36 - 40	3	7.3
Total	41	100

Hematological parameters

Hematological parameters before and after Feroxyl® supplementation in the study participants are shown in Table 2. At baseline, the mean Hb level was 9 g/dL at baseline, and the mean serum ferritin level was 7.4 µg/dL, respectively. These baseline values are below the normal ranges for pregnant women (>10.5 g/dL for Hb and >30 µg for serum ferritin) [3,4], confirming the diagnosis of IDA in the study participants. Pre-supplementation values for the other hematological parameters were also below their normal ranges for pregnant women (80-100 fL for MCV, 30-33 pg for MCH, and 32.4- 35.2 g/dL for MCHC, respectively), indicating hypochromic, microcytic anemia typical of iron deficiency.

After 6 weeks of Feroxyl® supplementation, improvements in hematologic parameters were observed. Mean Hb increased to 10.9 g/dL and serum ferritin increased to 26.6 µg/dL, indicating improvement in anemia and replenishment of iron stores. Mean MCV increased to 87.9 fL, reaching normal range, while mean MCH and MCHC increased to 29.2 pg and 32.7 g/dL, respectively, within or near normal range. All improvements in hematological parameters from baseline to follow-up were statistically significant ($p<0.001$).

Side effects

Table 3 shows the side effects experienced by the study participants following Feroxyl® supplementation. The majority of participants (70.7%) experienced no side effects, suggesting that Feroxyl® was well tolerated. The most commonly reported symptoms were heartburn (14.6%) and constipation (12.2%), which are typical of iron supplements, while only one participant reported nausea.

Table 1. *Hematological parameters before and after Feroxyl® supplementation among Libyan pregnant women with iron deficiency anemia (n=41).*

	Pre-supplementation	**Post-supplementation**			
Parameter	Mean ± SD	Mean ± SD	Lower 95% CI	Upper 95% CI	P-value
Hemoglobin (g/dL)	9.0 ± 0.6	10.9 ± 0.8	-2.1	-16.2	0.0001*
MCV (fL)	77.0 ± 5.6	87.9 ± 8.2	-13.1	-8.7	0.0001*
MCH (pg)	24.5 ± 2.8	29.2 ± 3.1	-5.5	-3.9	0.0001*
MCHC (g/dL)	28.6 ± 2.8	32.7 ± 2.3	-5.0	-3.3	0.0001*
Serum ferritin (µg/dL)	7.4 ± 3.7	26.6 ± 1.4	-23.2	-15.2	0.0001*

CI: Confidence interval; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; SD: Standard Deviation.
* A p-value <0.05 is considered statistically significant.

Table 3. *Distribution of Libyan pregnant women with iron deficiency anemia included in the study according to side effects of Feroxyl® supplementation (n=41).*

Side effect	**Frequency (n)**	**Percentage (%)**
No side effect	29	70.7
Heartburn	6	14.6
Constipation	5	12.2
Nausea	1	2.4
Total	41	100

Discussion

This study demonstrated significant improvements in hematological parameters in pregnant women with mild to moderate IDA after 6 weeks of Feroxyl® supplementation. All parameters, including Hb and serum ferritin levels, MCV, MCH, and MCHC, increased significantly ($p<0.001$) compared to baseline and were within or near normal ranges. The study also highlighted the tolerability of Feroxyl®, showing that 70.7% of participants experienced no adverse events after 6 weeks of supplementation.

In this study, the improvement in Hb levels was consistent with the results of other studies investigating the effects of ferrous bis-glycinate on IDA in pregnant women. A recent systematic review and meta-analysis reported significant increases in Hb levels in pregnant women and children after supplementation with ferrous bis-glycinate compared with other iron salts [11]. This suggests that ferrous bis-glycinate is particularly effective in improving Hb levels due to its superior bioavailability, reinforces the robustness of our findings and supports the use of Feroxyl® with ferrous bis-glycinate as an effective iron supplement in pregnancy.

Our study also showed a significant increase in ferritin levels after supplementation, indicating a significant improvement in iron stores in the study participants and the efficacy of Feroxyl® in replenishing iron stores. The most recent systematic review evaluating the effects of ferrous bis-glycinate supplementation showed that ferrous bis-glycinate supplementation resulted in a similar, but not significant, increase in serum ferritin in pregnant women compared to other iron supplements [11]. This discrepancy may be due to differences in study designs (clinical trials), study populations (children, pregnant women, adolescents, adults), doses of ferrous bis-glycinate administered (15-100 mg daily), and supplementation periods (4-22 weeks). In our study, the significant increase in ferritin levels after supplementation could be attributed to the specific supplementation protocol of Feroxyl® and the high adherence rate of our participants. Starting from very low baseline levels with a mean of 7.4 µg/dL may also explain the significant increase to 26.6 µg/dL in ferritin levels observed in our participants. Furthermore, a study conducted in 2018 showed that the lower the baseline Hb level, the greater the effect of ferrous bis-glycinate supplementation on ferritin levels [16], suggesting that participants' response to Feroxyl® in terms of Hg and ferritin levels depends on the initial level of deficiency. Our study did not compare participants with mild or moderate anemia in terms of response to Feroxyl® supplementation. Future studies should aim to stratify pregnant women by severity of anemia to better determine the magnitude of response to treatment and tailor supplementation strategies accordingly.

In addition to Hg and ferritin, our study showed significant improvements in other hematological parameters including MCV, MCH, and MCHC. This result indicates the correction of common features of IDA IDA, microcytosis and hypochromia, and supports the beneficial effect of Feroxyl® on the hematological health of pregnant women. Data on the effect of ferrous bis-glycinate on red blood cell indices are limited; however, a few studies have shown that treatment with ferrous bis-glycinate resulted in a significant increase in MCV in children with IDA [16] and in premenopausal women with iron deficiency without anemia (13). Our result is consistent with that of another randomized controlled trial that demonstrated an increase in MCV, MCH, and MCHC in pregnant women of 12-16 weeks' gestation who received oral iron as ferrous bis-glycinate in combination with folinic acid and multivitamins for the treatment of IDA for 6 months [17].

While our results showed significant increases in red blood cell indices, MCH and MCHC did not reach their normal ranges, which may be due to the short supplementation period of 6 weeks. Recommendations suggest that supplementation should be continued for approximately three months after normalization of Hb levels to fully restore iron stores [4,18]. Future research should aim to further investigate the mechanisms behind the differential effects of ferrous bis-glycinate on various hematological parameters, taking into account anemia severity and baseline hematological status, especially in pregnant women.

The present Feroxyl® intervention also includes vitamins C, B9, and B12, which play an important role in the metabolism and absorption of iron. In our study, the observed improvements in all hematological parameters following Feroxyl® supplementation may be due to the synergistic effects of ferrous bis-glycinate and the other vitamins. Specifically, the inclusion of vitamin C may have increased iron absorption from the supplement and helped mitigate some of the GI side effects. This effect of vitamin C has been well documented in many studies [19,20]. Vitamins B9 (folic acid) and B12 have been shown to enhance hematopoiesis and improve Hb levels [21], and are especially needed in pregnant women [22]. No studies have specifically evaluated this combination in IDA in pregnant women and direct comparisons cannot be made. However, our results are consistent with those of a randomized controlled trial of 120 pregnant women with IDA showing that supplementation with ferrous bis-glycinate combined with folinic acid and multivitamins (vitamins C, B1, B2, B6, B12, and calcium) significantly improved MCV, MCH, and MCHC, in addition to Hb and ferritin levels. Overall, this suggests that the combined supplementation in Feroxyl® may have additional benefits beyond iron bis-glycinate monotherapy, providing more effective restoration of iron stores and improvement in red blood cell indices. Future research and robust randomized controlled trials are needed to confirm our findings and further explore the synergistic effects of Feroxyl® in pregnant women and other populations with IDA.

In terms of side effects, our study found that the majority of our participants (70.7%) reported no side effects after 6 weeks of Feroxyl® supplementation, while a small proportion experienced nausea, heartburn, and constipation. Several studies have also shown that ferrous bis-glycinate has improved GI tolerability compared to other traditional iron supplements [10–13] because it is better absorbed by intestinal mucosal cells. This is due to its highly stable chemical composition, which often requires low therapeutic doses for treatment [12,16] and is not affected by iron absorption inhibitors, such as phytates [15,23]. Overall, the low incidence of side effects suggests that the use of Feroxyl® was well tolerated, which explains the high compliance rate among our participants and consequently the effective IDA treatment outcomes. Future studies are warranted to investigate the long-term effects of Feroxyl® and its impact on different populations to optimize IDA management.

Strengths and limitations

This study has several strengths. It provides valuable insights into the potential beneficial effects of a combination of ferrous bis-glycinate with folic acid and vitamins C and B12 in the management of IDA in pregnant women. The prospective observational design of the study allowed for real-world observation of participants and collection of more accurate and reliable data, which significantly reduced recall bias. Another strength is the high rate of adherence to follow-up, with 41 out of 50 participants adhering to the supplementation protocol and completing the study.

However, our results should be interpreted with several limitations. Data on pre-pregnancy anemia status, menstrual cycle and volume, dietary intake, underlying health conditions, and use of other iron supplements were not collected. This lack of data prevented adjustment for these confounding factors, which may have affected the hematologic parameters and obscured the specific effects of Feroxyl® supplementation. Other limitations of the study include the relatively small sample size of 41 participants, which may limit the generalizability of the results to all pregnant women with anemia, and self-reported adherence to the supplementation protocol, which may introduce bias and influence the results.

Conclusion

The results of this study demonstrate that Feroxyl® supplementation is effective and well tolerated in the treatment of IDA in pregnant women. After 6 weeks of supplementation, the significant improvements in Hb and serum ferritin levels, as well as MCV, MCH and MCHC, indicate correction of anemia and replenishment of iron stores. In addition, the low incidence of adverse events confirms the safety of Feroxyl® for the treatment of mild to moderate IDA in pregnant women.

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