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Original Research Article

Real-world evaluation of safety and effectiveness of ferrous bis-glycinate and its combination in pregnant women with iron deficiency anemia

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ABSTRACT

Background: Iron deficiency is the most common cause of anemia during pregnancy. It leads to adverse outcomes on maternal and infant morbidity/mortality. There is a reduction in hemoglobin levels due to an increase in iron demand during pregnancy. Many pregnant women have poor or depleted iron stores and the amount of iron from the diet together with mobilized stores from the body is insufficient to meet the maternal demands. To meet iron demands, regular iron supplementation is recommended. Conventional iron supplements report frequent gastrointestinal side effects. Therefore, this study aimed to evaluate the safety, effectiveness, tolerability, and compliance of ferrous bis-glycinate and it's combination for treating iron deficiency anemia during pregnancy.
Methods: This was a retrospective analysis of data collected from 34 obstetricians and gynecologists across India, on the use of ferrous bis-glycinate and it's combination as iron supplementation to pregnant women. The clinical records were analyzed for the objective i.e., rise in hemoglobin, safety, tolerability, and compliance.
Results: 374 completed case records forms were considered for the analysis. These pregnant women had taken supplementation with ferrous bis-glycinate and its combination for an average of 58.5 days. The use of ferrous bis-glycinate and it's combination improved mean hemoglobin concentration from 8.86 gm/dL to 11.27 gm/dL. With respect to safety, 97.6% of pregnant women did not report any adverse events. The remaining 2.4% had mild gastrointestinal side effects. Furthermore, 93% of pregnant women rated the tolerability as very good to good, and >98% of patients complied with >80% of treatment with ferrous bis-glycinate.
Conclusions: This retrospective analysis suggests that ferrous bis-glycinate and it's combination as iron supplementation in pregnancy is safe, effective, and well-tolerated.

Keywords: Iron deficiency anemia, Ferrous bisglycinate, Pregnancy, Hemoglobin

INTRODUCTION

Iron deficiency is a global public health challenge and the most common medical disorder during pregnancy.[1] It is the most common cause of anemia.[2] Anemia is defined as the reduction in an absolute number of circulating red blood cells (RBC)s, indirectly measured by a reduction in hemoglobin (Hb) concentration, hematocrit (Hct) or RBC count.[3] World Health Organization (WHO) has defined anemia as Hb of <11 g/dl but, during pregnancy, the definition of anemia differs, depending on the trimester (<11 g/dl in the first trimester, <10.5 g/dl in the second trimester, <11 g/dl in the third trimester).[3] Iron deficiency accounts for 75% of all types of anemia in pregnancy.[3] According to WHO, an estimated annual 1,15,000 maternal deaths occur globally due to iron-deficiency anemia.[2] In India, 45.7% of pregnant women in urban areas and 52.1% in rural areas have Hb levels <11 g/dl.[2] This leads to adverse outcomes on maternal morbidity/mortality and low birth weight that can contribute to the increasing percentage of infant mortality.[4] A reduction in Hb levels during pregnancy is more common because there is an increased iron demand due to normal physiological changes and many women have poor or depleted iron stores and the amount of iron absorbed from the diet, together with that mobilized from stores is insufficient to meet the maternal demands during pregnancy.[3] The total iron requirement is approximately 1.2 g in pregnancy, with the highest requirement in the third trimester, up to 7.5 mg daily.[5] Hemoglobin varies through trimesters and a physiological hemodilution occurs with a peak during 20-24 weeks of gestation.[3] Plasma volume increases by 50% during pregnancy along with a slight increase in RBC mass.[5] The disproportionate increase in plasma volume to RBC mass leads to decreased Hb and Hct levels, more evident from the second trimester to delivery.[5] Micronutrient deficiencies (e.g., vitamin B12 and folate) and inherited disorders that affect Hb synthesis and RBC survival, such as hemoglobinopathies, are also important causes.[2]

In a prospective, observational, and community-based study, anemia was estimated in 62.3% of women as the main pregnancy-related complication. In terms of maternal adverse effects, 3% had a difficult labour, 1.6% each had a postpartum hemorrhage and preeclampsia and 3.5% had abortions/stillbirth. The fetal complications included 25.5% low birth weight, 0.5% birth asphyxia, and 0.2% premature delivery. These findings show a clear relationship between anemia and pregnancy-related complication; thus, signifying the importance of its management.[6] As extra demand for iron is unmet through diet, regular iron supplementation is recommended during pregnancy. Although recommendations for iron supplementation differ according to region, the central for disease control and prevention recommends 30 mg/day of iron supplementation at a first prenatal visit and WHO recommends 30-60 mg/day for all pregnant women.[7]

Amongst the various available iron formulations, ferrous sulfate (32% elemental iron) and ferrous fumarate (33% elemental iron) are the most widely used.[8] Common challenge with conventional oral supplementation is significant variability in the bioavailability and tolerability of different iron forms.[9] The major disadvantage of traditional ferrous salts is the frequent gastrointestinal (GI) side effects such as nausea, vomiting, abdominal colic, and constipation which affects the patients' adherence to treatment and the efficacy of iron preparation.[9] Due to the GI side effects associated with conventional iron forms, alternatives have included iron chelates.[9] In light of this evidence, a retrospective study was designed to evaluate the safety, effectiveness, tolerability, and compliance of ferrous bis-glycinate and it's combination as iron supplementation for the treatment of iron deficiency anemia (IDA) during pregnancy.

METHODS

A retrospective analysis of data collected from the case record forms on the usage of combination of Ferrous bis-glycinate (60mg), zinc bis-glycinate (15 mg), folic acid (1 mg) and Methylcobalamin (500 mcg) supplementation (henceforth referred as ferrous bis-glycinate and it's combination) in pregnancy from 34 obstetricians and gynecologists across India between August 2022 and September 2022 was done. The case record forms included information on the history of gravidity, parity, current pregnancy gestational age; laboratory investigations including Hb at baseline and end of treatment; and adverse effects; prescribed dosage and duration of iron supplementation with ferrous bis-glycinate and it's combination along with other concomitant medication and compliance with therapy.

Data eligibility criteria

The clinical records of only those pregnant women were analyzed who had received ferrous bis-glycinate and it's combination as their iron supplement.

Data collection and analysis

The case record forms were collected from August 2022 to September 2022. These forms were analyzed for various parameters like demographics, dosage and duration of iron supplementation with ferrous bis-glycinate and its combination, Hb rise, tolerability, any adverse event, and compliance.

Study outcomes

The primary outcome included an evaluation of the safety profile including any adverse event experienced by the patients after administering iron supplementation with ferrous bis-glycinate and its combination. The secondary outcome was analyzing the effectiveness of ferrous bis-glycinate and its combination with respect to a rise in Hb

from baseline to end of therapy. Further, tolerability and compliance with treatment were assessed.

Statistical analysis

All continuous variables are summarized by the mean and standard deviation (SD) and categorical parameters are summarized by frequency (N) and percentage (%). A paired t test was used to compare the mean Hb level at baseline and end-line by mean and SD with statistical significance. The 95% confidence interval (CI) for the mean Hb gain was also reported. The drug's compliance, tolerability, and safety in terms of adverse events were evaluated by their respective proportions. Statistical software R version 4.2.1 was used for statistical analysis.

RESULTS

The 374 pregnant women included had a mean age of 28 years and a mean gestational age of 22.93 weeks. Ferrous bis-glycinate and it's combination were prescribed for an average duration of 58 days in the evaluable population as per medical records (Table 1).

Table 1: Baseline characteristics of pregnant women.

Variables	Mean (SD)
Age (year)	28.22 (5.8)
Body weight (kgs)	58.1 (10.83)
Gestational age (week)	22.93 (7.81)
Dose duration (days)	58.05 (51.89)

Safety

Of the 374 CRFs that were analyzed, adverse events were reported in 9 (2.41%) of the patients treated with ferrous bis-glycinate and it's combination. The most common adverse events reported were mild GI side effects like nausea and vomiting in 6 patients (67%), abdominal pain in one patient (11%), and GI disturbance in one patient (11%).

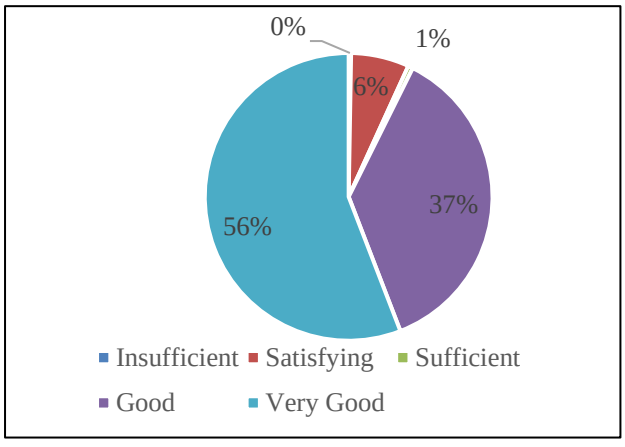

Figure 1: Tolerability of ferrous bis-glycinate and it's combination.

Tolerability and compliance

Out of the total cohort, 93% of patients rated very good to good tolerability with ferrous bis-glycinate and it's combination (Figure 1) and more than 98% of patients complied to >80% with the treatment.

Effectiveness

Mean Hb concentration: The baseline mean Hb concentration was 8.86±1.09 gm/dl which increased to 11.27±0.98 gm/dl post-treatment signifying an increase by 2.41 gm/dl ($p<0.001$) (Figure 2). The percentage of women with Hb level of more than 11g/dl after an average treatment duration of 58.5 days was 62.4%.

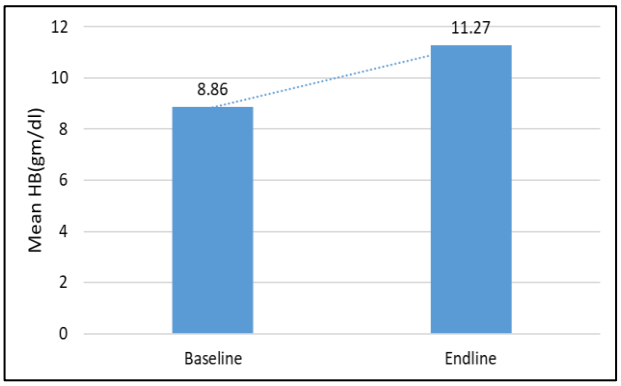

Figure 2: Mean Hb concentration between the baseline and end line.

DISCUSSION

Anemia during pregnancy is commonly seen among women in developing nations; suggesting that pre-existing iron stores are insufficient to fulfil the physiologic changes leading to increased iron requirement brought on by pregnancy.[10] Oral iron supplementation is frequently used to treat IDA, but not all patients benefit from this therapy. Most of the conventional oral iron preparation contain ferrous sulphate or ferrous fumarate. These commonly used oral iron supplement are associated with GI side effects like nausea, vomiting, abdominal pain, constipation etc. Moreover, the absorption from these preparations are also reduced by various ingredients present in the meals like phytates, polyphenols, calcium and tannins which leads to oxidation of ferrous to ferric form. Overall resulting in poor compliance and ineffectiveness.[10] Ferrous bis-glycinate is a highly stable amino acid chelate that is formed by the binding of two molecules of glycine to one Fe2+ atom. The molecule has a high bioavailability of iron since it is absorbed intact through the intestinal mucosal cells and then the iron is dissociated from ferrous bis-glycinate followed by distribution to the tissues. Thereby, also associated with fewer GI adverse effects.[11,12] Studies have shown that ferrous bis-glycinate has two-fold higher bioavailability and absorption compared to ferrous sulfate and ferrous fumarate.[9]

Table 1: Clinical trials with ferrous bis-glycinate compared to the present study.

Clinical trial	Trial design	Patient population	Treatment and duration	Key findings
Abbas et al.[11]	Randomized double-blind clinical trial	187 pregnant women at 14-18 weeks of gestation with Hb level between 7-10.9 g/dl	Group I received oral ferrous bis-glycinate tablets once daily for eight consecutive weeks and Group II received oral ferrous glycine sulfate for the same dose and duration	Mean increase in Hb in the ferrous bis-glycinate group was 2.48 g/dl while it was 1.32±0.18 g/dl in ferrous glycine sulfate group (p≤0.0001). Percentage of women with Hb level of more than 11 g/dl after 8 weeks was 89.2% in the ferrous bis-glycinate group vs 71.3% in the ferrous glycine sulphate group.
Youssef et al.[13]	Prospective longitudinal study	300 pregnant having Hb less than 9 gm/dl	Group I: received a combination of ferrous bisglycinate containing 27mg elemental iron once daily. Group II: received a combination of iron multi amino acid chelate containing 15mg elemental iron twice daily. Group III: received a combination of ferrous fumarate containing 66mg elemental iron three times daily. The treatment duration was for 4 weeks.	Mean Increase of 2.12 g/dl, 0.8 g/dl and 0.9 g/dl Hb in groups (I, II, III) respectively. The increase in ferritin with ferrous bis-glycinate was significantly more than other treatments. Compliance rate-96%
Makled et al.[14]	Randomised controlled trial	150 pregnant women having Hb 8-10.5 g/dl (14-18 weeks of gestation)	Ferrous bis-glycinate or Ferrous fumarate for 12 weeks.	Mean change in Hb in ferrous bis-glycinate group was 2.5±0.4 gm/dl while in FF group was 1.9±0.6 gm/dl. Compliance rate was higher in ferrous bis-glycinate group
Present study	Retrospective analysis	374 pregnant women	Mean follow-up duration of 58 days	Mean increase in Hb level 2.41 g/dl. Percentage of women with Hb level of more than 11 g/dl was 62.4%. Compliance rate >98%

Furthermore, Bumrungpert et al showed that ferrous bis-glycinate 30 mg was as effective as 120 mg of ferrous sulfate in preventing IDA and with more persistent correction of ferritin levels after a six-month follow-up.[9] The chelated iron preparation improved hematological parameters, iron absorption, quality of life, and birthweight in iron-deficient pregnant women compared to ferrous fumarate.[9] A comparison of a few previously done studies with ferrous bis-glycinate and the present one is depicted in (Table 1).

The currently available literature has shown that ferrous bis-glycinate and it's combination is a safe and effective treatment option for IDA, including preterm infants, children, pregnant women, cancer patients, and even inflammatory bowel disease patients. In this retrospective study, iron supplementation with ferrous bis-glycinate and it's combination did not report any adverse events in 97.5% of patients. It improved mean Hb concentration in pregnant women by 2.41 gm/dl. Further, it was found to be well tolerated in 93% of the patients and >98% patient complied to >80% of treatment. There was higher compliance seen due to the excellent tolerability profile of ferrous bis-glycinate and it's combination.

Strengths and limitations

The study, strength lies in assessing the safety and efficacy of ferrous bis-glycinate and it's a combination in pregnancy in a real-world setting. It gives insight into the change in Hb levels, adverse effects and compliance. The study has limitations namely the cohort size is small, and bias regarding the collected data.

CONCLUSION

To the best of our knowledge, this is the first real-world retrospective study of Ferrous bis-glycinate and its

combination in Indian women with IDA. Our findings suggest that supplementation with ferrous bis-glycinate and its combination can be a potential treatment option for the management of IDA as it has shown to be safe, effective, and very well tolerated from the clinical perspective.

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