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Original Research Article

Evaluation of safety and tolerability of iron amino acid chelate therapy in pregnant women

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ABSTRACT

Background: Anemia is a major health problem. Iron deficiency is the most common cause of anemia during pregnancy. It can be associated with increased preterm labor, preeclampsia, and maternal sepsis. It can also lead to fetal loss or even perinatal deaths. The aim of the study was to monitor the oral iron therapy [Iron Amino Acid Chelate (IAAC) equivalent to elemental iron 30 mg] administered according to hospital practice and to determine the safety, and tolerability of IAAC in pregnant women.
Methods: The data of pregnant women attending the outpatient department of the hospital for antenatal care between March 2020 and February 2021 and prescribed IAAC was retrospectively analyzed. It was of interest to note the changes in the Hemoglobin (Hb) levels and serum ferritin levels. These parameters were considered as the primary efficacy parameter and were analyzed by the paired t-test.
Results: The data indicated very well tolerance to IAAC preparation with increase in Hb levels. After 12 week of treatment, there were significant increases in hemoglobin levels with mean rise in Hb level was 7 to 9 gm/dL. A statistically significant difference was observed at the 4th, 8th, and 12th weeks from the baseline value to each evaluation in the Hb level due to the supplementation of oral iron. The change in the serum ferritin levels was found to be statistically significant at the 12th week from the baseline values. Most of the women tolerated the oral IAAC preparation
Conclusions: This retrospective analysis showcased a significant improvement in the Hb and serum ferritin levels of pregnant women after 12 weeks.

Keywords: Anemia, iron deficiency anemia, Iron amino acid chelate, Hemoglobin, pregnancy

INTRODUCTION

Iron deficiency continues to be an important cause of nutritional deficiency leading to anemia in addition to other deficiencies like folic acid or vitamin B12.[1] Iron Deficiency Anemia (IDA) cause an immense disease burden worldwide. Globally, there were over 1.2 billion cases of IDA in 2016. IDA is among the five greatest causes of years lived with disability globally, the leading cause of years lived with disability in Low- and Middle-Income Countries (LMICs) and is the leading cause of years lived with disability among women across 35 countries. Controlling anemia is a global health priority: WHO is aiming for a 50% reduction in anemia prevalence in women by 2025.[2]

As per World Health Organization (WHO), about 40% of all pregnant women across the globe are anemic.[1]

However, this prevalence is considerably high in India reaching up to 50–53%.[3,4]

Anemia is characterized by reductions in Hb concentration, red-cell count, or packed-cell volume. The mean minimum acceptable Hb level during pregnancy as suggested by WHO is said to be 11 g/dL. Despite considerable efforts by the Government of India over the past few decades to decrease its prevalence, anemia is still a significant health burden. A marginal reduction of 3.5% in IDA among all women in India from 2005–2006 to 2015–2016 has been observed despite all efforts. Of note, the occurrence of IDA in pregnant women is highest in India worldwide.[5,6]

IDA may also be associated with unfavorable maternal and perinatal outcomes like infections, cardiovascular complications, blood transfusions after deliveries in case of blood loss, low birth weight, anemia in newborns, decreased cognitive function, impeded neurodevelopment in infants, etc. It may also lead to maternal deaths based on the extent of iron deficiency. Iron supplementation in pregnancy has been proven to improve these outcomes as compared to placebo. Further, iron supplementation is especially important because the demand for iron increases from 0.8 mg/day in early pregnancy to 7.5 mg/day in late pregnancy with 4.4 mg/day over the whole course of pregnancy.[7,8]

The oral iron supplementation for IDA in pregnancy is usually provided until the Hb levels or the serum ferritin levels are in the normal range.8 Several oral preparations are available like ferrous salts, iron chelates, complexes of ferric hydroxide, or liposomal iron.[7,9,10]

Ferrous salts are said to be poorly absorbed from the intestine and thus providing low bioavailability. In addition, Gastrointestinal (GI) side effects are comparatively higher with these salts than iron chelates.[11,12] On the other hand, chelating iron with amino acids helps to increase its bioavailability and thus reducing the dose as well as time required to treat IDA.[9-12]

Single low doses of iron supplements (30 mg/day) are associated with less gastrointestinal side effects and lower hepcidin secretion, resulting in better treatment compliance and enhanced fractional absorption.[13]

As per previous studies, IAAC therapy was reported to have a more rapid effect with less GI tract side effects. After treatment with IAAC therapy containing 30 mg elemental iron, there were significant increases in Hb levels and lack of unwanted side-effects.[10,14]

Thus, it was of interest to note these observations in pregnant women in clinical practice at 4 weeks intervals to monitor the oral iron therapy (IAAC equivalent to elemental iron 30 mg) administered according to hospital practice and to determine the safety, and tolerability of IAAC.

METHODS

Study design

The electronic medical records of hospitals were visited between March 2020 to February 2021. Retrospectively, the data of pregnant women aged 20–35 years attending the outpatient antenatal care with a confirmed singleton pregnancy between 13–24 weeks was considered.

Pregnant women with Hb ranging from 8–11 g/dL with confirmed IDA with serum ferritin <15 µg/L and those who have prescribed oral IAAC preparation (equivalent to 30 mg elemental iron) and having at least two Hb and serum ferritin readings (before and after IAAC administration) were considered for analysis.

Data of pregnant women with reproductive age <20 years or ≥35 years, with multiple pregnancies, with anemia not linked to iron deficiency, with an allergy to iron derivatives, with other medical disorders (diabetes, tuberculosis, viral hepatitis, cirrhosis, malabsorption syndrome, cardiovascular disease, renal disease, autoimmune disease, cancer) or with suspected acute infection or any obstetric complicating factors like pregnancy-induced hypertension were excluded.

Patients with a history of chronic blood loss and those who had received parenteral iron treatment earlier were also excluded.

Analysis of investigations

The blood reports were obtained from the records and the following were considered for analysis— Complete blood count, Hb, and serum ferritin. CBC was used to confirm the diagnosis of IDA. Adverse effects were collected from patient charts retrospectively.

The analysis of investigations (Hb and Ferritin) was evaluated based upon the available data. The Hb and Ferritin at week 0 and post their treatment with IAAC was considered at the 4th, 8th, and 12th weeks.

The change in the Hb levels and serum ferritin levels were considered as the primary efficacy parameters while the secondary parameters included the cure rate and the occurrence of side effects during the study observational period.

Statistical analysis

The primary efficacy endpoints were analyzed by the paired t-test while the secondary endpoints were calculated as percentages. Data was statistically presented as mean ± Standard Deviation (SD), or frequencies (number of cases) or percentages. The $p<0.05$ was considered statistically significant. All statistical analysis was performed using GraphPad Prism (version 5.0).

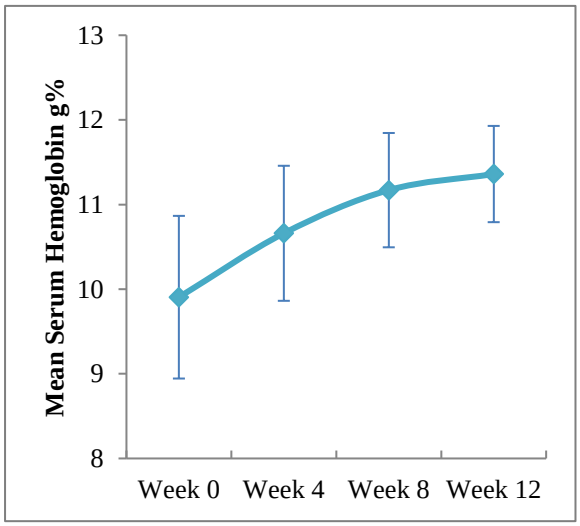
RESULTS

Medical records of 66 pregnant women who attended the antenatal care department of the hospital during an observation period of March 2020 to February 2021 were considered for analysis. The women with Hb in a range of 8-11 g/dl and who received an IAAC preparation were identified and considered for further analysis. Out of N=66 pregnant women; N=3 were found, who discontinued treatment due to side effects. The final observations were noted from N=63 pregnant women only. The mean maternal age was 27.87±3.11 years. The baseline data for Hb and serum ferritin levels are described in Table 1.

Table 1: Baseline characteristics of the 63 pregnant women.

Parameter	Value (n=63)
Age (years)	27.87±3.11
Hemoglobin (g/dl)	9.91±0.96
Serum ferritin (µg/l)	22.34±16.34

Note: Data presented as mean±standard deviation.



Note: Data presented as mean±standard deviation. *p<0.001 for the t-test considered significant.

Figure 1: Effect of administration of oral IAAC preparation on the serum Hb levels at 4th, 8th, and 12th week.

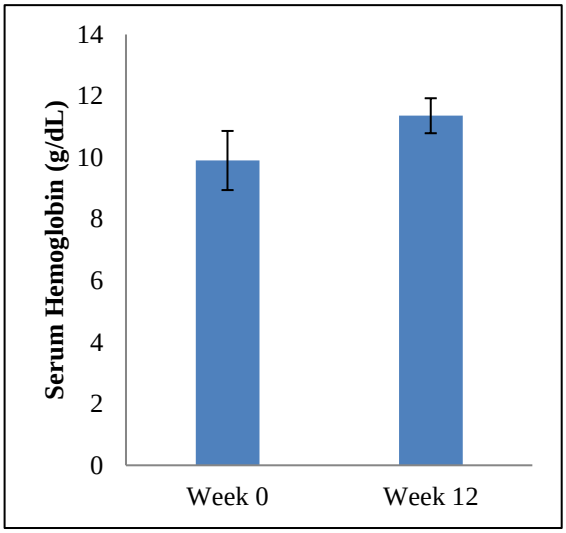
Change in hemoglobin levels

The observations evaluated at 12th week, showcased 72.7% women with Hb range (11.36±0.57) mg/dl, based on the WHO criteria of Hb level >11 g/dl found to be recovered. The mean difference in the Hb levels was found to be 1.51±1.13 from the baseline to the end of 12th week.

A statistically significant difference was observed at 4th, 8th, and 12th week from the baseline value to each evaluation in the Hb level due to the supplementation of oral iron as seen in Figure 1 and Figure 2.

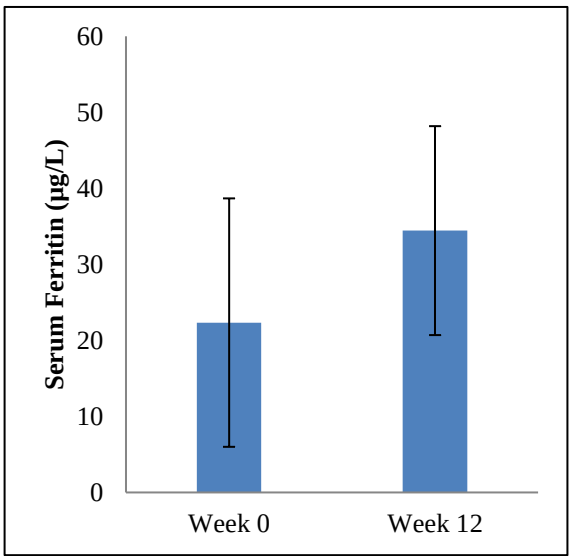
Change in serum ferritin levels

The mean difference in the serum ferritin levels was found to be 14.66±13.64 µg/l from the baseline to the end of the 12th week. The change in the serum ferritin levels was found to be statistically significant at the 12th week from the baseline values (Figure 3).



Note: Data presented as mean±standard deviation. * p<0.001 for the t-test considered significant.

Figure 2: Comparison of serum haemoglobin levels at baseline and at end on the study (12th week).



Note: Data presented as mean±standard deviation. * p<0.001 for the t-test considered significant.

Figure 3: Comparison of serum ferritin levels at baseline and at end on the study (12th week)

Secondary outcomes

Most of the women tolerated the oral IAAC preparation. Out of N=66 women, only N=2 women (3.03%) had shown vomiting while nausea and stomach discomfort was

observed with one woman (1.51%). Due to these side effects, these three women were not compliant with the therapy and observed discontinuation of treatment with therapy.

DISCUSSION

The retrospective data showcased the efficacy, safety, and tolerability of the oral IAAC preparation in the treatment of IDA or iron deficiency in pregnant women in India. IDA or iron deficiency in pregnancy is a significant and common prevalence among pregnant women in India. Several adverse maternal and perinatal outcomes have been shown due to IDA which could be improved upon iron supplementation.[3,7,8] However, a common consensus upon the inclusion of iron supplementation during pregnancy is still not present among different countries, especially among the developed and developing countries.[15] In Indian settings, iron supplementation is considered to be the best strategy to tackle this widespread prevalence of anemia in pregnancy.[16]

Oral iron supplementation is considered to be the first choice of agents to replenish the iron stores or treat iron deficiency owing to its simple absorption process in addition to being inexpensive and effective.[10,17] The most commonly applied oral iron preparations include ferrous salts but due to their low bioavailability as well as GI side effects, compliance to these agents has been found low.[17,18] This may be one of the reasons for the failure of various supplementation programs of the Government of India and needs to be addressed to reach the target of 32% by 2022 in pregnant women.[16]

Newer compounds of iron like chelates with amino acids are utilized currently as alternatives to ferrous salts both for prevention as well as treatment of IDA in pregnancy. Several studies have proven the upper hand of IAAC than ferrous salts in terms of bioavailability or tolerability.[9,10,12]

In a study conducted by Makled et al one hundred fifty pregnant women who met the criteria were randomized into 2 groups [IAAC group and Ferrous Fumarate (FF) group]. Hb level, blood indices, serum iron, and serum ferritin levels were measured in both groups at 4, 8, 12 weeks of treatment. The results showed a significant hematological improvement (mean Hb level, blood indices, serum iron, and ferritin levels) in both groups which were significantly higher in the IAAC group.[10]

Similarly, a study conducted by Abdel et al enrolled a total of N=150 pregnant women having iron deficiency anemia were randomized to receive either IAAC or FF for 12 weeks. Results showcased that the rise in Hb level after 4th, 8th, and 12th weeks of treatment was significantly faster in the IAAC group ($p \leq 0.001$).[9]

Consistent with previous studies, present observations also showcased significant improvement in the Hb levels at 4th, 8th, and 12th week with promising efficacy of oral IAAC preparation in pregnant women. Furthermore, serum ferritin levels are considered as a biomarker for the iron stores of the body in healthy women. A serum ferritin concentration <15 µg/L indicates low iron reserves which when combined with low Hb levels suggest IDA. In pregnant women, such ferritin levels are suggestive of starting iron supplements to retain a healthy pregnancy and its outcomes.[17]

Fe status biomarkers have also been used to estimate Fe absorption. Several attempts have been made to develop algorithms to estimate the bioavailability of Fe using Fe status biomarkers. In a study conducted by Valenzuela et al six hundred forty-six participants (582 women and 64 men) were selected from 40 Fe bioavailability studies and classified into four groups based on Fe status: normal Fe status (NIS), iron-depleted stores (IDS), Fe deficiency without anemia (IDWA), and Fe deficiency anemia (IDA). A standard dose of 3 mg of ferrous ascorbate was used in all studies. The absorption from FeRD% (Fe absorption of the reference dose) was calculated in each group and correlated with Fe status biomarkers. Study confirmed that a 40% Fe absorption of the reference dose in subjects with iron-depleted stores (IDS), and Fe deficiency without anemia (IDWA) is the most appropriate estimate to use as a reference in women of childbearing age.[19]

Our retrospective data also indicated a significant improvement in the serum ferritin levels at the end of the 12th week of therapy. Thus, suggesting that IAAC preparation could be effective in pregnancy to improve the reserve iron stores as well. These results are consistent with earlier studies done in the Indian population.[14,18]

Additionally, the results indicated that by the end of the 12th week, the cure rate (% of women with Hb levels >11 g/dL) was similar or better than the ferrous salts as reported in other studies.[9,10] This suggests the therapeutic efficacy of the IAAC preparation in correcting iron deficiency in pregnant women. Also, the improvement was seen between the 4th to 8th weeks of starting the therapy which was comparatively earlier than the ferrous salts as reported in previous studies.[10] This effect of rapid improvement may be helpful in women with iron deficiency who are detected late during their gestation period and required quick correction of anemia.

Such beneficial effect of IAAC preparation may be attributed to their better bioavailability as compared to other oral iron salts. The absorption of IAAC was found to be two times greater than the ferrous salts.[20] The iron salts usually ionize in the GI tract which leads to interaction with other anions like phosphates in the food. This leads to the complex formation which is not absorbed effectively and thus reduces bioavailability. However, IAAC is neutral that does not dissociate in the GI tract and thus able to cross the intestinal membrane effectively, improving the bioavailability.[9,21] Further, these chelates are transported by specific active transporters rather than passive

absorption of iron ions, adding to improvement in the bioavailability.[12]

Singhal et al conducted a prospective, randomized, comparative clinical study comprising of 250 antenatal women with Hb between 7-10 g%. The patients divided into five groups I, II,III,IV and IV of fifty each, by systematic randomization and were treated with ferrous sulphate (100 mg), ferrous fumarate (100 mg), ferrous ascorbate (100 mg), Iron Amino Acid Chelate (IAAC) equivalent to elemental iron 30 mg, sodium feredetate (33 mg) respectively. Hemoglobin estimation was done at day 0, 30 and 60 days and serum ferritin levels were done on day 0 and 60 days. There was significant and comparable rise in Hb on day 30 and day 60 in all the five groups ($p<0.001$). Ferrous ascorbate and Iron Amino Acid Chelate (IAAC) equivalent to elemental iron 30 mg showed significantly ($p<0.05$) more rise as compared to ferrous sulphate. Study showed that ferrous ascorbate and IAAC equivalent to elemental iron 30 mg are more effective than ferrous sulphate in treatment of iron deficiency anemia in pregnancy.[22]

Treatment of IDA with iron supplements can be divided into two phases: first the hemoglobin levels are restored and then the iron stores are replenished. However, to fully restore this mineral reserve, supplementation should continue for approximately 3 months after the normalization of Hb levels. Unfortunately, this strategy generally does not achieve the expected outcome due to patients' lack of adherence to treatment, mainly due to adverse effects such as epigastric discomfort, nausea, diarrhea or constipation.[23]

Further, the safety and tolerability of chelated iron preparations were reported to be better than the ferrous salts.[9,10,18] In a study conducted by Name et al, iron amino acid chelate shows good tolerability, exhibiting a lower incidence of adverse events when compared to ferrous sulfate, appears to be more effective in replenishing iron stores, favoring a reduction in required supplementation time. This represents an important advantage for treating IDA by reducing incomplete treatments that frequently occur for varied reasons.[23]

Similarly a study conducted by Sharma JB, et al. showed that rise in haemoglobin is significantly ($p<0.05$) higher than baseline Hb level, with greater tolerability and lack of unwanted side effects with IAAC. It showed better compliance and lack of unwanted side-effects hence it should be given as single tablet a day for prophylaxis and one tablet twice a day for therapeutic purpose.[14]

Our retrospective analysis supported these previous studies as only 3 women could not tolerate the preparation and discontinued the therapy. The presence of GI side effects was not very prevalent suggesting better tolerability of the preparation and thus improved adherence.

CONCLUSION

Thus, in conclusion, our observations showcased significant improvement in the iron status (Hb and serum ferritin levels) of the pregnant women after 12 weeks of administration of oral IAAC preparation. Further, IAAC preparation was found to be associated with fewer side effects. Hence, IAAC preparation has been suggested as an approach for increasing adherence and better patient compliance.

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