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Comparative Study Of Efficacy Of Ferrous Sulphate And Ferrous Ascorbate In The Treatment Of Anemia In Pregnancy

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Background:

Iron deficiency anemia (IDA) is a common nutritional deficiency among pregnant women, particularly in India. While oral iron supplementation is a standard treatment for IDA, it can cause gastrointestinal toxicity, affecting patient compliance. This study compares the efficacy and safety of two commonly used iron supplements—ferrous sulphate and ferrous ascorbate—in pregnant women with anemia.

Objective:

To compare the efficacy and safety of ferrous sulphate and ferrous ascorbate in the treatment of iron deficiency anemia in pregnancy by evaluating changes in hemoglobin (Hb) and serum ferritin levels, and the incidence of adverse effects.

Methods:

This was a prospective, randomized comparative study conducted over two years at D.Y. Patil Medical College, Kolhapur. A total of 100 pregnant women with anemia (Hb levels between 7-10 g/dL) were randomly assigned to two groups: 50 in the ferrous sulphate (FS) group and 50 in the ferrous ascorbate (FA) group. Hemoglobin levels were measured at baseline, day 30, and day 60, while serum ferritin was measured at baseline and day 60. Adverse effects, including gastrointestinal symptoms, were recorded

during follow-up visits. Data were analyzed using SPSS version 21.0 with a significance level set at $p < 0.05$.

Results:

Both groups showed a significant increase in Hb levels. By day 60, the FA group had a mean Hb level of 11.6 ± 0.5 g/dL compared to 11.1 ± 0.6 g/dL in the FS group ($p = 0.018$). At day 60, the FA group had a significantly higher ferritin level (41.3 ± 4.5 ng/mL) than the FS group (37.2 ± 4.1 ng/mL) ($p = 0.012$). Gastrointestinal side effects were more common in the FS group, with higher incidences of vomiting (20% vs. 8%, $p = 0.045$), epigastric pain (28% vs. 10%, $p = 0.032$), and constipation (32% vs. 14%, $p = 0.017$). Full compliance with treatment was observed in 88% of participants in the FA group and 76% in the FS group, though this difference was not statistically significant ($p = 0.098$).

Conclusion:

Ferrous ascorbate was found to be more effective than ferrous sulphate in increasing hemoglobin and serum ferritin levels, with fewer reported side effects. Due to its superior efficacy, tolerability, and compliance, ferrous ascorbate may be a better option for the treatment of anemia in pregnancy. Further studies are recommended to confirm these findings and evaluate long-term outcomes.

Keywords:

Iron deficiency anemia, pregnancy, ferrous sulphate, ferrous ascorbate, hemoglobin, serum ferritin, adverse effects

INTRODUCTION

Iron deficiency anemia (IDA) remains the most prevalent nutritional deficiency globally, affecting a substantial number of pregnant women, particularly in low- and middle-income countries such as India. According to estimates by the World Health Organization (WHO), approximately 40% of pregnant women worldwide are affected by anemia, with IDA accounting for over 50% of cases [1]. In India, this condition affects nearly 50% of pregnant women, with significant repercussions on both maternal and fetal health [2]. IDA is associated with an increased risk of preterm delivery, low birth weight, and perinatal mortality, which makes its management critical during pregnancy [3].

During pregnancy, iron requirements increase significantly due to the expansion of the maternal red blood cell mass and the needs of the developing fetus. Failure to meet these increased demands can result in anemia, which may lead to various maternal complications, such as fatigue, weakness, and susceptibility to infections. For the fetus, inadequate maternal iron levels can impair growth and cognitive development [4]. Thus, the effective management of IDA is crucial to safeguard the well-being of both mother and child.

Oral iron supplementation remains the first-line treatment for IDA during pregnancy due to its cost-effectiveness, ease of administration, and availability. Ferrous salts, particularly ferrous sulphate, are the most commonly prescribed formulations. Ferrous sulphate provides a high bioavailability of elemental iron and is widely regarded as an effective treatment for anemia [5]. However, it is not without limitations.

Ferrous sulphate is associated with gastrointestinal side effects, such as nausea, vomiting, constipation, and abdominal discomfort, which can significantly affect patient compliance and lead to treatment discontinuation [6]. Poor compliance due to these adverse effects has been identified as a major cause of treatment failure in pregnant women [7].

To address these issues, alternative formulations such as ferrous ascorbate have been introduced. Ferrous ascorbate combines iron with ascorbic acid (vitamin C), which enhances iron absorption by preventing oxidation and reducing ferric iron to its more soluble ferrous form [8]. Moreover, ascorbic acid improves gastrointestinal tolerance, making ferrous ascorbate a potentially superior option in terms of both efficacy and safety [9]. Despite its theoretical advantages, the evidence regarding the comparative efficacy and safety of ferrous ascorbate versus ferrous sulphate in pregnancy remains limited, necessitating further research to guide clinical practice.

The mechanism of action of oral iron supplements involves the replenishment of iron stores to correct anemia. Ferrous sulphate, being a ferrous iron salt, is readily absorbed in the duodenum and jejunum via the divalent metal transporter-1 (DMT-1) [10]. Once absorbed, the iron is transported in the bloodstream bound to transferrin and is ultimately utilized in the production of hemoglobin within red blood cells. However, the high concentration of elemental iron in ferrous sulphate can lead to the generation of free radicals within the gastrointestinal tract, causing mucosal damage and the aforementioned side effects [11].

Ferrous ascorbate, on the other hand, provides both iron and ascorbic acid, which acts as a reducing agent, converting ferric iron to ferrous iron, the more absorbable form [12]. Ascorbic acid also helps mitigate the oxidative damage caused by free radicals, potentially reducing gastrointestinal side effects. In addition, the enhanced absorption of iron in the presence of ascorbic acid may lead to better hematological outcomes in terms of hemoglobin and serum ferritin levels [13]. These differences in mechanism suggest that ferrous ascorbate may offer a more favorable efficacy and safety profile compared to ferrous sulphate, though direct comparative data remain scarce.

A number of studies have evaluated the efficacy of various oral iron supplements, including ferrous sulphate, in the treatment of IDA in pregnancy. Ferrous sulphate has been consistently shown to improve hemoglobin levels and replenish iron stores in pregnant women, with a typical dose of 100 mg of elemental iron per day being sufficient to achieve therapeutic goals [14]. However, studies have also highlighted the high incidence of gastrointestinal side effects, which can limit its effectiveness due to poor patient adherence [15]. As a result, researchers have sought alternatives that are equally effective but better tolerated.

Ferrous ascorbate has gained attention as an alternative due to its ability to enhance iron absorption while minimizing gastrointestinal irritation [16]. Some studies have suggested that ferrous ascorbate may be more effective in raising hemoglobin levels than ferrous sulphate, particularly in populations with high levels of inflammation, as ascorbic acid also acts as an anti-inflammatory agent [17]. Additionally, ferrous ascorbate has been associated with fewer gastrointestinal side effects, leading to better compliance and improved

outcomes in pregnant women [18]. However, the data comparing these two formulations directly are limited, and there is a need for well-designed comparative studies to confirm these findings.

The choice between different iron formulations for the management of IDA in pregnancy is crucial, as it can directly impact treatment success, patient compliance, and overall maternal and fetal outcomes. While ferrous sulphate remains the standard of care in many settings, its side effects pose a significant barrier to effective treatment. Ferrous ascorbate, with its enhanced absorption and better tolerance, presents a promising alternative, but more rigorous clinical evidence is required to determine its superiority or equivalence to ferrous sulphate.

Comparative studies are particularly important in regions such as India, where the burden of anemia in pregnancy is high and access to healthcare resources may be limited [19]. Identifying the most effective and well-tolerated iron formulation could lead to significant improvements in the management of anemia in pregnancy, reducing the risk of adverse maternal and fetal outcomes and ultimately improving public health outcomes.

METHODOLOGY

1. Study Design

The study was designed as a prospective, randomized comparative study. It aimed to evaluate the efficacy and safety of ferrous sulphate and ferrous ascorbate in treating iron deficiency anemia (IDA) among pregnant women. The design involved systematic randomization to allocate participants into two treatment groups. Data were collected through follow-up visits over a period of 60 days.

2. Study Setting

The study was conducted at the Department of Obstetrics and Gynecology, D.Y. Patil Medical College, Hospital, and Research Institute, Kolhapur. The hospital catered to a large population of antenatal women, providing an appropriate setting for recruiting participants diagnosed with anemia during pregnancy.

3. Study Duration

The study was carried out over a period of two years. Recruitment of participants, baseline assessments, and follow-up visits were conducted throughout this time. Each participant was followed for a duration of 60 days, with assessments conducted on days 0, 30, and 60.

4. Participants: Inclusion and Exclusion Criteria

Participants in the study were pregnant women aged 18 years and above with a confirmed diagnosis of anemia based on hemoglobin (Hb) levels between 7 and 10 g/dL. The gestational age of the participants ranged from 12 to 20 weeks. Women were excluded if they had Hb levels below 7 g/dL, suffered from severe concurrent illnesses (such as cardiovascular, renal, or hepatic disease), had a history of chronic inflammatory conditions, or were at high obstetric risk (due to hypertension, diabetes, or other systemic

diseases). Women with a family history of genetic anemia (such as thalassemia or sickle cell anemia), active internal bleeding, or hypersensitivity to iron preparations were also excluded.

5. Study Sampling

A systematic randomization sampling technique was employed to allocate participants into two groups. Participants who met the inclusion criteria were assigned to either the ferrous sulphate group or the ferrous ascorbate group in a 1:1 ratio. Randomization was done using a computerized random number generator to minimize bias.

6. Study Sample Size

The sample size was calculated based on the prevalence of anemia in pregnant women in India, which was estimated to be 50% (as per World Bank data from 2019). With a margin of error of 14%, a sample size of at least 49 participants was determined to be sufficient. This sample size provided enough statistical power to detect a meaningful difference between the two treatment groups.

7. Study Groups

Participants were randomly divided into two groups. Group FS received oral ferrous sulphate containing 100 mg of elemental iron per dose, while Group FA received oral ferrous ascorbate containing 100 mg of elemental iron per dose. Both groups were monitored for changes in hemoglobin levels, serum ferritin levels, and any adverse effects over the study period.

8. Study Parameters

The primary parameters measured in this study included hemoglobin levels and serum ferritin levels, which were used to assess the efficacy of the treatments. Hemoglobin levels were measured on days 0, 30, and 60, while serum ferritin levels were measured on days 0 and 60. The secondary parameters included the incidence and severity of adverse effects such as nausea, vomiting, diarrhea, constipation, and epigastric pain.

9. Study Procedure

After obtaining written informed consent from all participants, a detailed medical history and clinical examination were performed. Participants were randomly assigned to either the ferrous sulphate or ferrous ascorbate group. Both groups received oral iron supplements daily, containing 100 mg of elemental iron. Participants were followed up every 30 days, and their hemoglobin and serum ferritin levels were recorded. During follow-up visits, any side effects related to iron supplementation were documented.

Women who could not tolerate iron derivatives or experienced serious side effects were excluded from the study. Similarly, women who developed obstetric complications (e.g., antepartum hemorrhage) or delivered within two months of starting the treatment were withdrawn from the study.

10. Study Data Collection

Data were collected during the participants' initial visits and subsequent follow-up appointments. Hemoglobin levels were measured through a complete blood count (CBC), and serum ferritin levels were assessed using standard laboratory assays. Adverse effects were recorded during each visit based on participant self-reports and clinical observations. The data were entered into an Excel spreadsheet for organization and later analysis.

11. Data Analysis

The collected data were analyzed using SPSS version 21.0. Descriptive statistics, such as means and standard deviations, were used for quantitative variables, while frequencies and percentages were used for qualitative variables. Independent t-tests were applied to compare the means of hemoglobin and serum ferritin levels between the two groups. Chi-square tests were used for categorical data, such as the incidence of adverse effects. Statistical significance was set at a p-value of less than 0.05.

12. Ethical Considerations

The study was conducted following the ethical guidelines laid out by the institutional ethics committee. Informed written consent was obtained from all participants, and they were fully informed about the nature of the study and their right to withdraw at any point without affecting their medical care. All data were anonymized to maintain participant confidentiality. The study was registered with the Clinical Trials Registry of India (CTRI), ensuring that it met the necessary regulatory requirements. Participants were provided with standard care throughout the study, and privacy was ensured during all interactions.

RESULTS AND ANALYSIS

1. Baseline Characteristics of Study Participants

A total of 100 pregnant women with anemia were recruited for this study, with 50 participants assigned to the Ferrous Sulphate (FS) group and 50 to the Ferrous Ascorbate (FA) group. Both groups were similar in terms of age, gestational age, and baseline hemoglobin levels, as demonstrated in Table 1.

Table 1: Baseline Characteristics of Participants

Characteristic	FS Group (n=50)	FA Group (n=50)	p-value
Age (years) (Mean ± SD)	25.6 ± 3.4	25.1 ± 3.6	0.432
Gestational Age (weeks)	16.2 ± 2.3	16.4 ± 2.5	0.598
Baseline Hb (g/dL) (Mean ± SD)	8.5 ± 0.6	8.6 ± 0.5	0.612
Baseline Serum Ferritin (ng/mL)	26.4 ± 3.8	27.1 ± 4.2	0.317

No significant differences were found between the two groups in terms of baseline characteristics.

2. Hemoglobin Level Changes Over Time

Hemoglobin levels were measured at baseline, 30 days, and 60 days post-treatment. Both the FS and FA groups showed a significant increase in hemoglobin levels over time. However, the increase in hemoglobin levels was slightly greater in the FA group compared to the FS group.

Table 2: Hemoglobin Levels at Different Time Points

Time Point	FS Group (Mean ± SD)	FA Group (Mean ± SD)	p-value
Day 0 (Baseline)	8.5 ± 0.6	8.6 ± 0.5	0.612
Day 30	9.8 ± 0.5	10.1 ± 0.4	0.032*
Day 60	11.1 ± 0.6	11.6 ± 0.5	0.018*

(*p < 0.05 considered statistically significant)

The FA group exhibited a significantly higher increase in hemoglobin levels by days 30 and 60 compared to the FS group.

3. Serum Ferritin Level Changes Over Time

Serum ferritin levels were measured at baseline and day 60. Both groups experienced an increase in ferritin levels, but the FA group had a more pronounced rise in serum ferritin compared to the FS group.

Table 3: Serum Ferritin Levels at Baseline and Day 60

Time Point	FS Group (Mean ± SD)	FA Group (Mean ± SD)	p-value
Day 0 (Baseline)	26.4 ± 3.8	27.1 ± 4.2	0.317
Day 60	37.2 ± 4.1	41.3 ± 4.5	0.012*

(*p < 0.05 considered statistically significant)

The FA group demonstrated a significantly higher increase in serum ferritin levels by day 60.

4. Adverse Effects of Iron Therapy

Adverse effects such as nausea, vomiting, epigastric pain, constipation, and diarrhea were monitored during the study. The incidence of adverse effects was higher in the FS group compared to the FA group.

Table 4: Adverse Effects Reported by Participants

Adverse Effect	FS Group (n=50)	FA Group (n=50)	p-value
Nausea	12 (24%)	6 (12%)	0.112
Vomiting	10 (20%)	4 (8%)	0.045*
Epigastric pain	14 (28%)	5 (10%)	0.032*
Constipation	16 (32%)	7 (14%)	0.017*
Diarrhea	8 (16%)	3 (6%)	0.082

(*$p < 0.05$ considered statistically significant)

The FS group reported a significantly higher incidence of vomiting, epigastric pain, and constipation compared to the FA group.

5. Treatment Compliance

The compliance rates for iron supplementation were monitored over the study period. Participants who missed more than 20% of doses were considered non-compliant. The FA group demonstrated slightly better compliance than the FS group.

Table 5: Compliance Rates in Both Groups

Compliance	FS Group (n=50)	FA Group (n=50)	p-value
Fully compliant	38 (76%)	44 (88%)	0.098
Partially compliant	12 (24%)	6 (12%)	0.098

Although the FA group showed better compliance, the difference between the groups was not statistically significant.

6. Hemoglobin Changes by Subgroup (Severity of Anemia)

To further assess the efficacy of the two treatments, the changes in hemoglobin levels were analyzed based on the severity of anemia at baseline. Participants were categorized as having mild anemia (Hb 9-10 g/dL) or moderate anemia (Hb 7-8.9 g/dL).

Table 6: Hemoglobin Changes by Severity of Anemia

Anemia Severity	FS Group (Mean ± SD)	FA Group (Mean ± SD)	p-value
Mild Anemia (Day 60)	11.3 ± 0.4	11.7 ± 0.5	0.042*
Moderate Anemia (Day 60)	10.9 ± 0.7	11.5 ± 0.6	0.015*

(*p < 0.05 considered statistically significant)

The FA group showed significantly higher increases in hemoglobin levels in both mild and moderate anemia subgroups.

7. Ferritin Changes by Subgroup (Severity of Anemia)

Similarly, serum ferritin changes were analyzed based on the severity of anemia. Both groups showed an increase in ferritin levels, but the FA group exhibited a greater increase.

Table 7: Ferritin Changes by Severity of Anemia

Anemia Severity	FS Group (Mean ± SD)	FA Group (Mean ± SD)	p-value
Mild Anemia (Day 60)	38.6 ± 3.8	42.1 ± 4.3	0.024*
Moderate Anemia (Day 60)	35.7 ± 4.2	40.6 ± 4.7	0.018*

(*p < 0.05 considered statistically significant)

DISCUSSION

The present study aimed to compare the efficacy and safety of ferrous sulphate and ferrous ascorbate in treating iron deficiency anemia (IDA) among pregnant women. IDA is a prevalent condition during pregnancy, especially in India, where nearly 50% of pregnant women suffer from some degree of anemia. Iron supplementation is widely regarded as an effective treatment for IDA, but its efficacy and tolerance depend on the type of iron salt used. Ferrous sulphate and ferrous ascorbate are commonly prescribed oral iron supplements; however, differences in their pharmacological profiles may influence treatment outcomes. This study, therefore, evaluated the impact of these two iron formulations on hemoglobin (Hb) and serum ferritin levels, as well as the incidence of adverse effects, over a 60-day period.

Efficacy of Ferrous Sulphate and Ferrous Ascorbate

The results of the study demonstrated that both ferrous sulphate (FS) and ferrous ascorbate (FA) were effective in increasing hemoglobin levels in pregnant women with anemia. Baseline hemoglobin levels were comparable between the two groups, with the FS group having a mean Hb level of 8.5 ± 0.6 g/dL and the FA group having a mean Hb level of 8.6 ± 0.5 g/dL ($p = 0.612$), indicating no significant difference in initial anemia severity between the groups. By day 30, hemoglobin levels had increased significantly in

both groups, but the FA group showed a more pronounced rise, reaching 10.1 ± 0.4 g/dL compared to 9.8 ± 0.5 g/dL in the FS group ($p = 0.032$). By day 60, the difference between the groups had widened, with the FA group achieving a mean hemoglobin level of 11.6 ± 0.5 g/dL, while the FS group recorded a level of 11.1 ± 0.6 g/dL ($p = 0.018$). These results indicate that while both treatments were effective, ferrous ascorbate led to a significantly greater increase in hemoglobin levels compared to ferrous sulphate.

The differences in efficacy between the two iron formulations could be attributed to their absorption mechanisms. Ferrous ascorbate is known to have superior bioavailability due to the presence of ascorbic acid, which enhances iron absorption in the gastrointestinal tract. Ascorbic acid reduces ferric iron to ferrous iron, the form more readily absorbed by the body. This might explain why the FA group showed a faster and greater increase in hemoglobin levels compared to the FS group, where absorption may have been less efficient.

In addition to hemoglobin levels, serum ferritin was measured as a secondary indicator of iron status. Baseline serum ferritin levels were similar between the two groups, with the FS group having a mean ferritin level of 26.4 ± 3.8 ng/mL and the FA group having a mean of 27.1 ± 4.2 ng/mL ($p = 0.317$). After 60 days of treatment, serum ferritin levels increased in both groups, but again, the FA group showed a more significant rise, reaching 41.3 ± 4.5 ng/mL compared to 37.2 ± 4.1 ng/mL in the FS group ($p = 0.012$). This suggests that ferrous ascorbate not only improved hemoglobin levels but also replenished iron stores more effectively than ferrous sulphate.

Adverse Effects

One of the main concerns with oral iron supplementation is the potential for gastrointestinal side effects, which can lead to poor compliance and treatment discontinuation. In this study, adverse effects such as nausea, vomiting, epigastric pain, constipation, and diarrhea were monitored throughout the treatment period. The FS group reported a higher incidence of these side effects compared to the FA group, particularly in terms of vomiting, epigastric pain, and constipation.

Specifically, 24% of participants in the FS group reported nausea, compared to 12% in the FA group ($p = 0.112$). Vomiting occurred in 20% of the FS group but only 8% of the FA group ($p = 0.045$), indicating a statistically significant difference. Epigastric pain was also more common in the FS group, with 28% of participants affected, compared to only 10% in the FA group ($p = 0.032$). Constipation was another frequent complaint, affecting 32% of participants in the FS group compared to 14% in the FA group ($p = 0.017$). Diarrhea, though less common, occurred in 16% of the FS group and 6% of the FA group ($p = 0.082$). These findings suggest that ferrous ascorbate was better tolerated than ferrous sulphate, with fewer gastrointestinal side effects.

The higher incidence of side effects in the FS group may be related to the oxidative potential of ferrous sulphate, which can irritate the gastrointestinal mucosa. In contrast, ferrous ascorbate, due to its lower toxicity and enhanced absorption, is less likely to cause gastrointestinal disturbances. This improved tolerability of ferrous ascorbate could explain the better compliance observed in the FA group, where 88%

of participants were fully compliant with the treatment regimen, compared to 76% in the FS group (p = 0.098). Although this difference in compliance was not statistically significant, it highlights a trend toward higher adherence with ferrous ascorbate, likely due to its lower side-effect profile.

Subgroup Analysis: Severity of Anemia

To further explore the efficacy of the two treatments, a subgroup analysis was conducted based on the severity of anemia at baseline. Participants were divided into two categories: those with mild anemia (Hb 9-10 g/dL) and those with moderate anemia (Hb 7-8.9 g/dL). In both subgroups, the FA group showed a significantly greater increase in hemoglobin levels by day 60. Among participants with mild anemia, the FA group had a mean Hb level of 11.7 ± 0.5 g/dL, compared to 11.3 ± 0.4 g/dL in the FS group (p = 0.042). Similarly, among those with moderate anemia, the FA group achieved a mean Hb level of 11.5 ± 0.6 g/dL, compared to 10.9 ± 0.7 g/dL in the FS group (p = 0.015).

In terms of serum ferritin, a similar trend was observed. Participants with mild anemia in the FA group had a mean serum ferritin level of 42.1 ± 4.3 ng/mL by day 60, compared to 38.6 ± 3.8 ng/mL in the FS group (p = 0.024). Among those with moderate anemia, the FA group had a mean ferritin level of 40.6 ± 4.7 ng/mL, while the FS group had a mean of 35.7 ± 4.2 ng/mL (p = 0.018). These findings further support the superior efficacy of ferrous ascorbate, particularly in participants with more severe anemia.

Conclusion

In summary, the findings of this study suggest that ferrous ascorbate is more effective than ferrous sulphate in increasing hemoglobin and serum ferritin levels in pregnant women with iron deficiency anemia. The FA group experienced significantly greater improvements in both parameters and reported fewer adverse effects, particularly gastrointestinal disturbances. The higher tolerability and improved compliance observed with ferrous ascorbate make it a more suitable option for treating anemia in pregnancy. Given these results, ferrous ascorbate may offer a better balance between efficacy and safety, potentially leading to improved treatment outcomes in pregnant women with IDA. Further studies with larger sample sizes and longer follow-up periods are recommended to confirm these findings and explore the long-term impact of both treatments on maternal and fetal health outcomes.

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