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Efficacy and Tolerability of Twice Daily Versus Alternate Day Iron Supplementation during Pregnancy with Mild To Moderate Iron Deficiency Anaemia

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Abstract

Background: Iron deficiency anemia (IDA) is the most prevalent cause of anemia globally, affecting over 2 billion people, with pregnant women being particularly at risk. Traditional iron supplementation often leads to gastrointestinal side effects, prompting the exploration of alternate dosing strategies.

Aim: To evaluate and compare the efficacy and tolerability of twice-daily versus alternate-day oral iron supplementation in pregnant women with mild to moderate iron deficiency anemia.

Methods: A randomized controlled trial was conducted at the Department of Obstetrics and Gynecology, SMS Medical College, Jaipur, involving 90 pregnant women (aged 20–35 years) with mild to moderate IDA. Participants were randomized into two groups: Group A received twice-daily ferrous sulfate (120 mg elemental iron), and Group B received alternate-day ferrous sulfate (120 mg elemental iron). Hemoglobin (Hb), serum ferritin, and reticulocyte hemoglobin equivalent (RET-He) levels were measured before and after 42 days of treatment. Side effects were recorded.

Results: Group A showed a significant increase in Hb from 9.1±1.8 to 9.8±2.03 gm%, while Group B showed a more substantial increase from 8.9±1.01 to 11.4±1.1 gm% ($p<0.0001$). Serum ferritin levels rose significantly more in Group B (44.5±9.06 mcg/L) compared to Group A (29.1±10.9 mcg/L) ($p<0.0001$). Both groups showed improvements in RET-He levels, with Group B showing a higher mean increase ($p<0.0001$). Side effects were similar in both groups.

Conclusion: Alternate-day iron supplementation is more effective in improving anemia, with better serum ferritin levels and enhanced erythropoiesis. It also shows comparable tolerability, making it a viable treatment for mild to moderate IDA in pregnant women.

Keywords: Iron deficiency anemia, iron supplementation, pregnancy, reticulocyte hemoglobin

equivalent, alternate-day dosing, ferrous sulfate, gastrointestinal side effects.

Introduction

Iron deficiency anemia (IDA) is the most prevalent cause of anemia worldwide, affecting over 2 billion people, accounting for more than 30% of the global population.[1] Its prevalence varies, ranging from 1–2% in men, 2–5% in females, 9–11% in adolescent females, and 17–31% in pregnant women. In developing countries, IDA affects up to 80% of pregnant women, increasing maternal mortality and work impairment.[2] It is linked to perinatal complications such as pre-eclampsia, low birth weight, prematurity, and perinatal mortality.6 Socioeconomically disadvantaged populations are disproportionately affected by IDA.

Iron is crucial for red blood cell production, DNA synthesis, and energy metabolism. IDA symptoms include fatigue, restless leg syndrome, and pica. It also reduces aerobic capacity, work tolerance, and cognitive functions such as attention and memory.[3] The WHO defines anemia as hemoglobin <12.0 g/dL in females and <13.0 g/dL in males. Serum ferritin is the most predictive diagnostic marker, with levels <30 mcg/L indicating iron deficiency.[4]

Pregnant women have high physiological iron demands that are difficult to meet through diet alone, making iron supplementation essential. Oral iron therapy remains the standard treatment, with ferrous gluconate, sulfate, and fumarate being the most commonly used formulations. Ferrous iron is more bioavailable than ferric iron, as it is better absorbed by enterocytes. Standard therapy involves 3–4 iron tablets daily. However, recent research suggests alternate-day dosing enhances iron absorption by preventing hepcidin-mediated iron inhibition.[5]

Oral iron supplementation is often associated with gastrointestinal side effects such as nausea, constipation, diarrhea, and altered gut flora. Hepcidin, a key regulator of iron homeostasis, inhibits iron absorption by binding to ferroportin. In iron deficiency, hepcidin levels decrease, enhancing iron uptake through divalent metal transporter 1 (DMT1).[6] Hepcidin levels strongly correlate with serum ferritin.

Studies show intermittent iron supplementation effectively prevents and treats mild IDA. A randomized controlled trial demonstrated that alternate-day dosing results in higher cumulative iron absorption than daily dosing.[7]

This study aims to evaluate the efficacy and tolerability of twice-daily versus alternate-day oral iron supplementation in pregnant women with mild to moderate IDA.

Material and Methods

This randomized controlled trial at the Department of Obstetrics and Gynecology, SMS Medical College, Jaipur, was conducted from April 2021 onwards. A prospective study, it included 90 mild to moderate anemic pregnant women (20–35 years, 14–16 weeks live pregnancy, no prior iron supplementation) in each group, calculated at a 95% confidence level and 80% study power (Randomized controlled trial of twice daily versus alternate day oral iron therapy in the treatment of iron deficiency anemia.[8] The null hypothesis stated no difference in hemoglobin rise between twice-daily and alternate-day iron therapy, while the alternate hypothesis suggested a significant difference.

Selection Criteria

Inclusion Criteria: Pregnant women aged 20–35 years, between 14–16 weeks of live pregnancy, who have not received prior iron supplementation and have mild to moderate iron deficiency anemia (Hb 7–11.0 gm%, MCV <80 fL, S. Ferritin <15 mcg/L) were included.

Participants had to provide consent for randomization and not be enrolled in any other study.

Exclusion Criteria: Women with other known causes of anemia, including dimorphic anemia, folate or vitamin B12 deficiency anemia, sideroblastic anemia, thalassemia, sickle cell anemia, aplastic anemia, hemolytic anemia, or anemia of chronic disease, were excluded. Additional exclusions included those with malabsorption syndromes (celiac disease), prior gastric or bariatric surgery, HIV, liver disease, or kidney disease.

Methodology

Ethical Approval & Screening: Approval was obtained from the RRB and Institutional Ethics Committee. All antenatal women at 14–16 weeks of pregnancy were screened through routine investigations and ultrasonography. Those with singleton live pregnancies and Hb (7–11 gm/dl), MCV (<80 fL), and S. Ferritin (<15 mcg/L) were recruited, applying inclusion and exclusion criteria. Informed written consent was obtained.

Study Procedure: A detailed history, general physical, and obstetric examination were conducted. Routine blood tests (CBC, PBF, S. Ferritin, MCV, RET-He, RFT, LFT, S. Electrolytes, Blood Sugar, HIV, VDRL, Anti-HCV, HBsAg) and USG were performed. Participants were randomized by the flip coin method into two groups:

Group A – Twice-daily ferrous sulfate (120 mg elemental iron)

Group B – Alternate-day two tablets of ferrous sulfate (120 mg elemental iron)

Each participant received 82 ferrous sulfate tablets (government supply) and was instructed on proper intake, avoiding tea, coffee, dairy, and antacids around medication time.

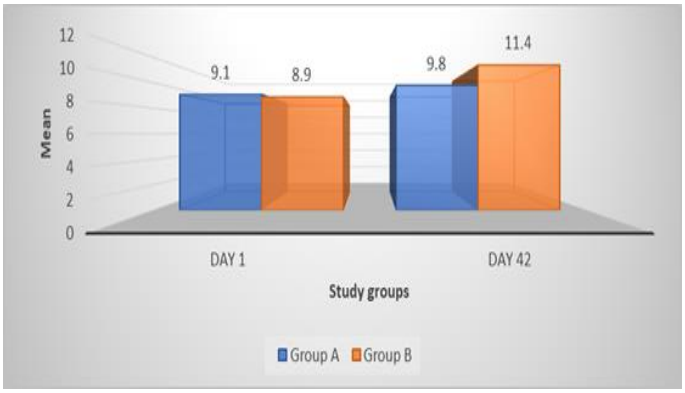
Statistical Analysis: Data were summarized as mean ± standard deviation. Group differences were analyzed using an unpaired *t*-test, while categorical data were compared using the chi-square test. A *p*-value <0.05 was considered statistically significant.

Observations and Results

The majority of patients were aged 19–22 years (71.5% in Group A, 58.8% in Group B), with a mean age of 22.2 years. Most were Hindu (56.8% in Group A, 58.8% in Group B) and from urban areas (67.6% in Group A, 70.59% in Group B). The majority were gravida 3 (34.31% in Group A, 28.4% in Group B).

The majority of patients were at 15–16 weeks gestation (52.94% in Group A, 50.0% in Group B). Most had hemoglobin levels of 8–9.9 gm% (66.6% in Group A, 55.8% in Group B), with a mean Hb of 9.1±1.8 gm% in Group A and 8.9±1.01 gm% in Group B). After 42 days, 38 patients in Group B reached Hb 11–11.9 gm%, while 41 achieved >12 gm%, whereas no patients in Group A had Hb >12 gm%.

Figure 1: Mean of change in Hemoglobin.



In Group A, mean hemoglobin increased from 9.1±1.8 to 9.8±2.03 gm%, which was statistically significant (*p*=0.009). In Group B, it rose from 8.9±1.01 to 11.4±1.1 gm%, a highly significant increase (*p*<0.0001).

Most patients had initial S. ferritin levels of 13–15 mcg/L (72.5% in Group A, 70.5% in Group B), with mean levels of 13.15±0.94 and 13.17±0.7, respectively. A good rise in S. ferritin (>20 mcg/L) was seen in

69.6% of Group A and 97% of Group B. Mean S. ferritin increased to 29.1±10.9 in Group A and 44.5±9.06 in Group B, a highly significant difference (p<0.0001).

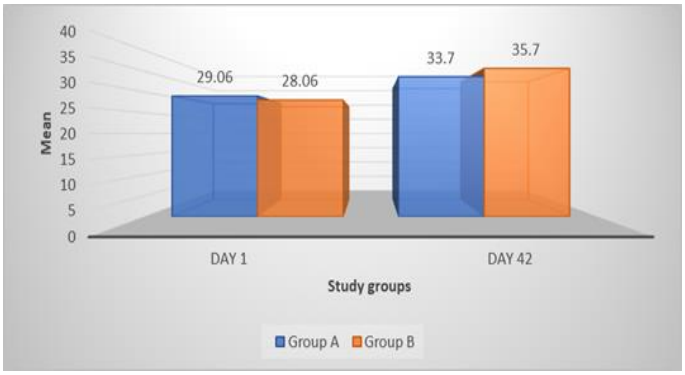
Table 1: Mean of change in S. FERRITIN (mcg/l).

Study groups	Day 1	Day 42	P-value
Group A	13.15± 0.9	29.1± 10.9	<0.0001
Group B	13.17± 0.7	44.5± 9.06	<0.0001

After 42 days of iron therapy, the mean rise in S. ferritin was 29.1±10.9 in Group A and 44.5±9.06 in Group B, a highly significant difference (p<0.0001).

At recruitment, 43.13% of Group A and 42.17% of Group B had RET-He levels between 30–34, while 56.8% in Group A and 58.8% in Group B had levels below 29. The mean RET-He was 27.25±2.8 in Group A and 28.06±3.8 in Group B, with no significant difference (p=0.08). After 42 days, 74.5% in Group A and 53.92% in Group B had RET-He levels up to 34, while higher values were observed in 25.49% of Group A and 46.07% of Group B.

Figure 2: Mean of change in RET He.



The mean RET-He increased significantly in both groups. In Group A, it rose from 29.06±2.8 to 33.7±2.9 (p<0.0001), while in Group B, it increased from 28.06±3.8 to 35.7±2.7 (p<0.0001). This indicates that both daily and alternate-day iron supplementation regimens were effective in improving anemia.

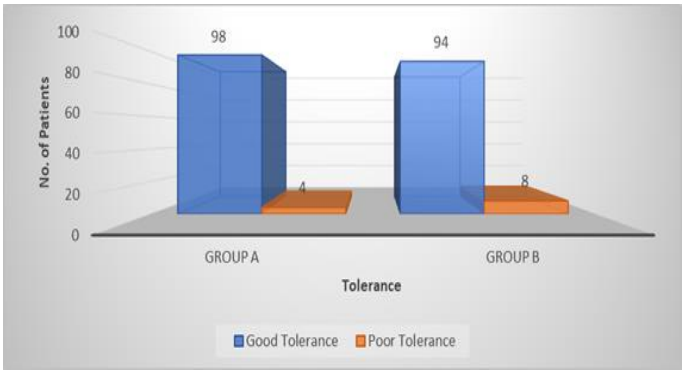
Table 2: Distribution of study population according to Side effects

Side effects	Group A		Group B		P-value
	No. of patients	Percentage	No. of patients	Percentage	
Nausea	20	19.61	20	19.61	0.42
Vomiting	9	8.82	17	16.67	
Diarrhoea	16	15.69	12	11.76	
Constipation	5	4.90	6	5.88	
Pain Abdomen	2	1.96	5	4.90	
Altered Taste	4	3.92	7	6.86	
Gabrahat/chakkar	4	3.92	8	7.84	

Side effects were reported in both groups, with nausea being the most common (19.6% in both). Vomiting was noted in 8.82% of Group A and 16.6% of Group B. Other side effects in Group A included diarrhea (15.6%), constipation (4.9%), abdominal pain (1.96%), altered taste (3.92%), and *ghabhrahat* (3.92%). In Group B, diarrhea (11.76%), constipation (5.8%), abdominal pain (4.9%), altered taste (6.86%), and *ghabhrahat* (7.84%)

were observed. Although Group B had slightly more side effects, the difference was not statistically significant (p = 0.42, NS).

Figure 3: Distribution of study population according to the tolerance of Ironsupplementations.



Tolerance to iron therapy was poor in 4 (3.92%) patients in Group A and 8 (7.84%) patients in Group B.

Discussion

Anemia is the most common nutritional deficiency in pregnancy worldwide, affecting 62–88% of pregnant women in India. Despite iron supplementation programs since 1971, the issue persists, largely due to poor compliance from gastrointestinal side effects. Daily iron intake raises plasma hepcidin levels for up to 24 hours, inhibiting ferroportin channels and reducing iron absorption the following day. This explains the better absorption and significant hemoglobin rise observed in Group B with alternate-day therapy. Given the limited success of large-scale programs, WHO, UNICEF, and the International Nutritional Anaemia Consultative Group are considering intermittent iron supplementation as a therapeutic approach.[8]

In our study, mean hemoglobin on day 1 was 9.1±1.8 mg/dl (Group A) and 8.9±1.01 mg/dl (Group B), rising to 9.8±2.03 mg/dl and 11.4±1.1 mg/dl on day 42, respectively, with a statistically significant difference ($p < 0.0001$). Similarly, Kaundal R et al.[9] found a faster Hb rise in the BD (twice-daily) arm at 3 weeks, but by 6 weeks, the AD (alternate-day) arm showed comparable results. Their findings differed from ours. Agarwal S K et al.[10] reported no significant Hb increase in daily or weekly iron groups, contrasting with our study, where alternate-day therapy showed better efficacy.

In our study, mean S. Ferritin on day 1 was 13.15±0.9 mcg/l (Group A) and 13.17±0.7 mcg/l (Group B), rising to 29.1±10.9 mcg/l and 44.5±9.06 mcg/l on day 42, with a statistically significant difference ($p < 0.0001$). Agarwal S K et al.[10] found no significant difference in serum ferritin rise between daily and weekly supplementation, unlike our study. Zlotkin S et al.[11] reported a significant ferritin increase after 2 months of treatment ($p < 0.0001$), though baseline levels were higher than expected, likely due to concurrent infections.

In our study, mean RET-He on day 1 was 27.25±2.8 (Group A) and 28.06±3.8 (Group B), rising to 33.7±2.9 and 35.7±2.7 on day 42, with a statistically significant difference ($p < 0.0001$). Pasupathy E et al.[12] found no significant difference in reticulocyte count changes between alternate-day (0.74%) and daily-dose (0.78%) groups ($p = 0.97$). Mehta S et al.[13] concluded that daily iron therapy increases hepcidin more than alternate-day dosing, reducing iron absorption and hemoglobinization, leading to a lesser rise in RET-He. RET-He is an early marker of iron incorporation, reflecting enhanced erythropoiesis after supplementation.

In our study, 19.6% of patients in both groups experienced nausea, followed by vomiting in 8.82% (Group A) and 16.6% (Group B). Diarrhea and constipation were reported by 15.6% and 4.9% in Group A, and 11.76% and 5.8% in Group B, respectively. Agarwal S K et al.[10] found severe GI intolerance in more women in the daily group (n=7) than in the weekly group (n=2), with two discontinuing iron due to severe vomiting. Kaundal R et al.[9] reported a better adverse

event profile in the AD arm, with nausea being more frequent in the BD arm.

In our study, 96.08% of patients in Group A and 92.16% in Group B had good tolerance, while 3.91% in Group A and 7.84% in Group B had poor tolerance. Kaundal R et al.[9] found that AD dosing leads to a gradual increase in hemoglobin despite delivering half the elemental iron compared to BD dosing. This approach may be suitable for mild anemia, while moderate anemia treatment can be individualized based on the need for faster response or better tolerance.

Conclusion

Iron deficiency, one of the most prevalent medical disorders, remains under-evaluated despite its global impact, especially in developing countries. Higher iron needs in expectant mothers, newborns, children, and teenagers, along with low iron bioavailability in food, contribute to widespread deficiency. Our study concludes that alternate-day single-tablet dosing (120 mg elemental iron) is effective. Daily iron therapy increases hepcidin more significantly, reducing iron absorption from subsequent doses and leading to lesser hemoglobinization, as reflected by a lower rise in RET-He. RET-He, a real-time marker of iron incorporation, indicates enhanced erythropoiesis with alternate-day dosing.

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