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Effect of Daily Dose Vs Alternate Day Dose Oral Iron on Improvement in Hemoglobin Levels in Iron Deficiency Anemia in First and Second Trimester of Pregnancy

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ABSTRACT

Background: Iron deficiency anemia (IDA) is a common and significant complication during pregnancy, necessitating effective and well-tolerated treatment strategies. While daily oral iron supplementation is a standard approach, its comparative efficacy against alternate-day supplementation remains an area of ongoing research. **Objective:** To compare the efficacy of daily oral iron dose and alternate oral iron dose for the treatment of IDA in first and second trimester of pregnancy. **Study Design:** Randomized controlled trial. **Duration and Place of Study:** The study was conducted from May 2024 to November 2024 at the Obstetrics and Gynecology Department, Hayatabad Medical Complex, Peshawar. **Methodology:** A total of 296 pregnant women aged 15–40 years with singleton pregnancies (≤24 weeks gestation) and diagnosed with IDA were randomized into two groups. Group A received daily ferrous fumarate (350 mg) for eight weeks, while Group B received the same dose on alternate days. Weekly monitoring was performed, and hemoglobin levels were reassessed after eight weeks. Efficacy was defined as a hemoglobin increase of ≥2 g/dL. **Results:** In Group A, 28.4% of patients achieved the defined efficacy, compared to 13.5% in Group B (p=0.002). Stratification analyses revealed significant efficacy differences favoring Group A in patients aged 15–30 years (p=0.004), with gestational age ≤15 weeks (p=0.005), and BMI >25 (p=0.012). No significant differences were observed for older patients, later gestational age, or lower BMI categories. **Conclusion:** Daily oral iron supplementation is significantly more effective than alternate-day dosing in treating IDA during pregnancy, particularly in younger women.

INTRODUCTION

Iron deficiency anemia (IDA) still remains the most common nutritional disorder in pregnancy, posing serious risks to maternal and fetal health.[1] Generally, anemia results from dietary deficiency of iron supply because of increased demands or due to some prevalent incident of anemia.[2] Iron dosage during the pregnancy phase in women is given particularly to provide for metagalaxy and placentome development and further blood volume inside the body of a pregnant woman. If left untreated, IDA may be further complicated by preterm birth, low birth weight, and postpartum depression. The healthy pregnancy outcome and prevention of the long-term consequence for both mother and child depend on the early diagnosis and effective treatment of IDA.[3]

Due to its easy accessibility, affordability, and safety, oral iron supplementation is considered the first line of treatment for IDA in pregnancy.[4] It works by replenishing iron stores and improving the production of hemoglobin, which is very important in carrying oxygen in the blood. The response of oral iron therapy depends on various factors, including adherence to treatment, severity of anemia, and bioavailability of the iron formulation used. In fact, numerous studies have reported significant increases in hemoglobin following chronic iron therapy and most subjects begin to realize their improvement within 4-6 weeks of aggressive intervention.[5] Occasional adherence might be impaired depending on adverse side effects like gastrointestinal malaise including nausea, constipation, and/or dyspepsia.[6]

The frequency of the iron supplement has been a study in depth as to optimizing efficacy and minimizing side effects.[7] Traditional recommendations have included daily dosing, although recent studies indicate that an alternate-day dosing could achieve the same goal in improving hemoglobin levels in pregnant women with IDA. Thus, this mode of dosing allows better iron absorption due to the body's natural regulation of hepcidin, a hormone inhibiting iron absorption.[8] This strategy might have lesser gastrointestinal adverse effects, and therapeutic compliance may improve with better patient acceptance. In comparison studies, it was mentioned that either

regimen yielded improvements in the patients' hemoglobin levels, but the alternate-day regimen could be another choice which would offer convenience without compromising the program of patient clinical outcomes.[9] This way, an appropriate plan takes into account the personal needs of pregnant women in various settings. A study conducted by von Siebenthal HK and colleagues demonstrated that the effectiveness of administering iron daily reached 11.4%, whereas using an alternate-day iron regimen resulted in only 3% efficacy among women experiencing iron deficiency anemia.[10]

The increase in the prevalence of iron deficiency anemia during pregnancy, as well as the necessity to further improve the treatment regimen for better maternal and fetal outcomes, has thus warranted the need for this study. While daily oral iron supplementation is one of the commonly recommended treatments, it is associated with frequent side effects that contribute to poor adherence, which may result in its limitation to being ineffective. Recent data indicate that the alternate-day dosing may increase iron absorption and reduce adverse effects, but comparative data on efficacy in improving hemoglobin levels during pregnancy is still scanty.

METHODOLOGY

This study was conducted as a randomized controlled trial over a period of ten months from May 2024 to November 2024 following the approval of the study protocol. The research took place in the Obstetrics and Gynecology Department at Hayatabad Medical Complex, Peshawar. A total of 296 participants were recruited, with 148 assigned to each group. The sample size was determined using a 95% confidence interval, 5% significance level, and 80% statistical power, considering the effectiveness rates of 11.4% for daily iron supplementation compared to 3% for alternate-day supplementation in women diagnosed with iron deficiency anemia.[10]

Women aged 15 to 40 years, with singleton pregnancies confirmed via ultrasound, gestational age ≤24 weeks based on last menstrual period or dating scan, and meeting the operational definition for iron deficiency anemia were included. Participants were excluded if they had hereditary or hemolytic anemia, inflammatory bowel or celiac disease, inherited bleeding disorders, active bleeding, were in their third trimester, or had a history of missed abortion.

Demographic information, including age, gestational age, parity and body mass index (BMI) was recorded. Random allocation into two groups was achieved using block randomization.

Group A (n=148) received one ferrous fumarate tablet (350 mg) daily for eight weeks, while Group B (n=148) received the same dosage on alternate days over the same duration. All participants were monitored weekly, and hemoglobin levels were reassessed after eight weeks to determine efficacy. Efficacy was defined as a hemoglobin increase of ≥2 g/dL, as per the operational definition.

Statistical analysis was carried out using SPSS software version 26. Continuous variables were summarized as mean ± standard deviation or median with interquartile ranges for non-normal data (Shapiro-Wilk test applied for normality assessment). Categorical variables were presented as frequencies and percentages. The chi-square test was used to compare efficacy between the groups, with a p-value ≤ 0.05 considered statistically significant.

RESULTS

In a sample of 296 patients equally divided into Group A and Group B, the mean age was 27.040 ± 4.45 years in Group A and 25.817 ± 6.25 years in Group B, while the mean gestational age was 16.270 ± 4.82 weeks and 15.641 ± 5.39 weeks, respectively. Group A had a mean parity of 2.067 ± 1.04 compared to 1.425 ± 1.07 in Group B. The BMI in Group A averaged 27.095 ± 1.74 kg/m^2, slightly lower than 27.609 ± 2.60 kg/m^2 in Group B as shown in Table-I.

Table I

Demographics of the patients (n=296)

Demographics	Group A n=148 Mean±SD	Group B n=148 Mean±SD
Age (years)	27.040±4.45	25.817±6.25
Gestational age (weeks)	16.270±4.82	15.641±5.39
Parity	2.067±1.04	1.425±1.07
BMI (Kg/m^2)	27.095±1.74	27.609±2.60

In terms of efficacy, 28.4% of patients in Group A and 13.5% in Group B demonstrated efficacy, with a significant difference (p=0.002) as shown in Table-II.

Table II

Comparison of efficacy between the two groups (n=296)

Efficacy	Group A n=148 n (%)	Group B n=148 n (%)	P value
Yes	42 (28.4%)	20 (13.5%)	
No	106 (71.6%)	128 (86.5%)	0.002
Total	148 (100%)	148 (100%)	

Stratification analyses revealed that in patients aged 15–30 years, Group A had 29.5% efficacy compared to 13.7% in Group B (p=0.004), whereas among those aged 31–40 years, the difference was not significant (p=0.212). For gestational age ≤15 weeks, efficacy was significantly higher in Group A (31.5%) compared to Group B (13.4%, p=0.005), but no significant difference was noted for gestational age >15 weeks (p=0.170). Among patients with parity 0–2, Group A showed a significantly higher efficacy of 29.5% versus 14.2% in Group B (p=0.004), while for parity >2, the difference was not significant (p=0.134). For BMI ≤25, the difference in efficacy between groups was not significant (p=0.079), but for BMI >25, Group A had significantly higher efficacy (29.0%) compared to Group B (15.5%, p=0.012) as shown in Table-III.

Table III

Stratification of Efficacy Based on Demographic Variables Across Groups

Demographics variables	Group	Efficacy		P-value
		Yes (n, %)	No (n, %)	
Age 15–30 years	A	33 (29.5%)	79 (70.5%)	0.004
	B	16 (13.7%)	101 (86.3%)	
Age 31–40 years	A	9 (25%)	27 (75%)	0.212
	B	4 (12.9%)	27 (87.1%)	

GA ≤ 15 weeks	A	29 (31.5%)	63 (68.5%)	0.005
	B	11 (13.4%)	71 (86.6%)	
GA >15 weeks	A	13 (23.2%)	43 (76.8%)	0.170
	B	9 (13.6%)	57 (86.4%)	
Parity 0-2	A	31 (29.5%)	74 (70.5%)	0.004
	B	18 (14.2%)	109 (85.8%)	
Parity >2	A	11 (25.6%)	32 (74.4%)	0.134
	B	2 (9.5%)	19 (90.5%)	
BMI ≤25	A	4 (23.5%)	13 (76.5%)	0.079
	B	2 (6.2%)	30 (93.8%)	
BMI >25	A	38 (29.0%)	93 (71.0%)	0.012
	B	18 (15.5%)	98 (84.5%)	

DISCUSSION

The study aimed to compare the efficacy of daily oral versus alternate-day oral iron in treating iron deficiency anemia (IDA) during the first and second trimesters of pregnancy. The results demonstrated significantly higher efficacy in Group A (28.4%) compared to Group B (13.5%), particularly among patients with lower gestational age (≤15 weeks), lower parity (0–2), and higher BMI (>25). These findings can be attributed to the more consistent replenishment of iron stores with daily dosing, which may enhance iron absorption by saturating transferrin receptors and maintaining steady-state iron levels. Conversely, the lower efficacy observed with alternate-day dosing may be due to suboptimal iron availability and reduced stimulation of erythropoiesis over time, highlighting the physiological necessity of consistent supplementation during the heightened metabolic demands of pregnancy. These findings are consistent with Wali et al. [11] where daily intravenous iron achieved greater hemoglobin improvements (3.8 g/dL) compared to alternate or intramuscular dosing (2.4 g/dL and 1.4 g/dL, respectively). Both studies suggest that frequent iron supplementation addresses increased metabolic demands in early pregnancy more effectively than less frequent regimens. Our study also found significant efficacy differences in women with higher BMI (>25), where Group A had a 29.0% efficacy compared to 15.5% in Group B (p=0.012). This aligns with findings by Peña-Rosas et al. [12] who reported that daily iron supplementation improved maternal iron status more effectively than alternate regimens. However, the similarity extends to gastrointestinal side effects, which were noted more frequently with daily regimens in both studies.

The results from Stanworth et al. [13] contrast with our findings, as their pilot study observed better adherence in alternate-day regimens (89.6%) compared to daily dosing (72.3%), suggesting that reduced frequency enhances compliance. Although the mean hemoglobin levels in their study improved more in the daily group, the adherence gap might explain the lower efficacy of alternate-day supplementation in our study, despite comparable tolerability.

Pasupathy et al. [14] reported no significant differences in hemoglobin increases between daily (1.36 ± 1.51 g/dL) and alternate-day regimens (1.05 ± 1.34 g/dL, p=0.47), suggesting alternate-day therapy as a viable option. However, their study did not include stratification based on gestational age or BMI, potentially underestimating subgroup-specific differences observed in our study.

Sadaf et al. [15] found greater hematologic improvements with daily iron in non-anemic women, with significantly higher hemoglobin (13.2 ± 0.9 g/dL vs. 12.9 ± 0.95 g/dL) and hematocrit levels (35.857 ± 0.87% vs. 32.857 ± 0.91%). These results align with our findings that daily regimens offer superior outcomes in improving iron status, particularly in early pregnancy and among women with higher metabolic demands due to increased BMI or parity.

Safarzadeh et al. [16] and our study share similar observations regarding efficacy in relation to dosing frequency, but their study noted fewer gastrointestinal side effects with alternate-day therapy. This suggests a trade-off between efficacy and tolerability, emphasizing the need for individualized treatment plans based on patient-specific factors such as adherence potential and side effect profiles.[17]

Collectively, the evidence suggests that daily iron supplementation is more effective for improving hematologic outcomes in high-demand subgroups such as younger pregnant women, those in early gestation, and those with higher BMI. Alternate-day regimens, while potentially better tolerated, may not consistently meet the physiological demands of pregnancy. Differences in adherence rates, patient characteristics, and study methodologies likely account for the variability across studies. While alternate-day regimens may offer better tolerability, their efficacy appears to be suboptimal in certain subgroups such as those with early gestational age, higher BMI, or greater parity. This highlights the need for individualized treatment strategies tailored to specific patient profiles and clinical scenarios.

However, this study has several limitations. It was conducted at a single center, which may limit the generalizability of the findings. Additionally, the follow-up period was relatively short, precluding an assessment of long-term outcomes such as postnatal maternal and neonatal iron status. The study also relied on adherence self-reports, which may introduce reporting bias. Future multicenter trials with longer follow-up durations and objective measures of adherence could provide more comprehensive insights.

CONCLUSION

Our study has concluded that daily oral iron supplementation is significantly more effective than alternate-day dosing in treating iron deficiency anemia during pregnancy. The findings highlight that daily regimens better address the heightened metabolic demands of pregnancy, particularly in subgroups such as those with early gestational age, higher BMI, and lower

parity. While alternate-day dosing may improve tolerability, it is less effective in achieving optimal hematologic outcomes, emphasizing the importance of individualized approaches to iron supplementation during pregnancy.

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