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RESEARCH ARTICLE
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HAEMATOLOGICAL RESPONSE TO DAILY VERSUS INTERMITTENT IRON SUPPLEMENTATION IN MILD TO MODERATE IRON DEFICIENCY ANAEMIA DURING PREGNANCY: A PROSPECTIVE COMPARATIVE STUDY

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ABSTRACT

Background: Iron deficiency anaemia (IDA) is one of the most common medical disorders encountered during pregnancy and remains a major contributor to maternal morbidity in low- and middle-income countries. In India, more than half of pregnant women are anaemic, necessitating effective and acceptable iron supplementation strategies. Daily oral iron is the standard regimen; however, gastrointestinal side effects and poor adherence have prompted interest in intermittent dosing. Evaluating hematological response to different supplementation schedules is essential for optimising antenatal care.

Objectives: To compare the hematological response—specifically changes in hemoglobin and hematocrit—to daily versus twice-weekly oral iron supplementation among pregnant women with mild to moderate IDA.

Methods: This prospective, randomized comparative study was conducted at the Department of Obstetrics and Gynaecology, PGIMS Rohtak, Haryana, over 14 months. A total of 200 antenatal women between 14–24 weeks of gestation with mild to moderate IDA were enrolled and randomized into two groups: Group A received daily oral iron (100 mg elemental iron + 500 mcg folic acid), and Group B received twice-weekly supplementation with the same formulation. Clinical evaluation and laboratory investigations, including hemoglobin and hematocrit estimation, were performed at enrolment and every 4 weeks until delivery. Compliance and adverse effects were assessed at each visit. Data were analysed using unpaired t-test and Chi-square test, with $p < 0.05$ considered statistically significant.

Results: Baseline characteristics were comparable between groups. Hemoglobin increased steadily in both groups, with no statistically significant difference at any time point ($p > 0.05$). Percentage improvement in hemoglobin was also similar across follow-ups. Hematocrit showed a parallel rising trend in both groups, with a significant difference observed only at 16 weeks, where Group B

demonstrated a higher percentage increase ($p = 0.013$). Overall, both regimens produced comparable hematological improvement, indicating non-inferiority of twice-weekly dosing.
Conclusion: Daily and twice-weekly oral iron supplementation regimens yield similar hematological outcomes in pregnant women with mild to moderate IDA. Given comparable efficacy, reduced pill burden, and potential for improved adherence, twice-weekly iron supplementation presents a practical alternative to daily dosing in antenatal care programs, particularly in resource-limited settings.

Keywords: Iron deficiency anaemia, Pregnancy, Daily iron supplementation, Twice-weekly iron, Hematological response, Hemoglobin, Antenatal care

INTRODUCTION

Anaemia in pregnancy remains one of the most widespread public-health challenges globally, with significant implications for maternal well-being, fetal development and overall population health. The World Health Organization (WHO) estimates that nearly 37% of pregnant women worldwide are anaemic, making it one of the leading indirect causes of maternal morbidity.[1] Iron Deficiency Anaemia (IDA) accounts for the majority of these cases, representing approximately half of all anaemia burden in pregnancy.[2]

Anaemia in pregnancy is defined by WHO as a haemoglobin concentration <11 g/dL, reflecting inadequate oxygen-carrying capacity of the blood.[3] During pregnancy, expanding plasma volume, increased red-cell mass, and the demands of the growing fetus elevate physiological iron requirements substantially. Total iron demand during pregnancy approaches 1,000 mg, including requirements for fetal growth, placenta, maternal erythropoiesis, and basal losses.[4] However, typical dietary intake and absorption are often insufficient to meet these demands. Non-heme iron absorption is limited to 5–15% depending on dietary composition, inflammation, and gastrointestinal conditions.[5]

In India, the burden of anaemia is particularly high due to nutritional inadequacies, infections, poor dietary diversity, and socioeconomic factors. According to NFHS-5 (2019–21), the prevalence of anaemia among pregnant women in India is 52.2%, while in Haryana it is 47.6%, reflecting a substantial regional health challenge.[6] The Ministry of Health and Family Welfare (MoHFW) identifies IDA as a leading modifiable factor contributing to adverse maternal outcomes.[7] As a result, the Government of India recommends universal iron and folic acid (IFA) supplementation under the National Iron Plus Initiative (NIPI).[8]

Oral iron supplementation remains the first-line treatment for mild to moderate IDA in pregnancy because it is cost-effective, widely available, safe and capable of restoring haemoglobin in most cases. Standard daily oral iron therapy typically increases haemoglobin over 4–6 weeks, with iron stores gradually replenished thereafter.[9] However, daily dosing may be associated with gastrointestinal side-effects such as nausea, constipation, metallic taste and epigastric discomfort, contributing to poor adherence.[10]

A growing body of research highlights that daily dosing might also be constrained by physiological regulation of iron absorption. Hepcidin, the key iron-regulatory hormone, rises after iron ingestion and reduces absorption from subsequent doses for up to 24 hours or more.[11] This suggests that providing iron on alternate or intermittent schedules may theoretically enhance absorption and reduce mucosal stress. Experimental evidence has shown that alternate-day dosing leads to higher fractional iron absorption compared to consecutive daily dosing.[12]

Intermittent iron supplementation regimens — including twice-weekly or weekly dosing — have thus emerged as potential alternatives, especially in resource-limited settings. Studies evaluating intermittent supplementation among pregnant women have yielded mixed results. Some randomized trials found comparable rises in haemoglobin between daily and intermittent iron administration, with significantly fewer side-effects in the intermittent group.[13,14] A WHO evidence review concluded that intermittent iron therapy may be considered in populations where daily dosing poses challenges, though evidence quality remains moderate.[15]

In an Indian study from North India, intermittent iron dosing produced non-inferior hematologic outcomes compared to daily therapy in mild anaemia, with better compliance and fewer adverse events.[16] Another trial involving antenatal women showed that haemoglobin rise after 8 weeks did not differ significantly between intermittent and daily regimens.[17] Conversely, some research reports slightly superior haemoglobin increments with daily therapy, though tolerability was lower.[18]

Given these divergent findings and the substantial IDA burden in India, the optimal dosing schedule for oral iron supplementation remains an area of active investigation. In regions such as Haryana — including institutions like the Department of Obstetrics and Gynaecology, PGIMS, Rohtak — anaemia continues to be a frequently encountered antenatal problem, underscoring the need for context-specific evidence guiding treatment strategies.

The hematological response to iron supplementation—measured through haemoglobin concentration, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), and serum ferritin—offers a direct assessment of the effectiveness of any regimen. Evaluating how daily and twice-weekly supplementation compare specifically in terms of hematological improvement can help refine local clinical protocols, improve compliance, reduce treatment burden, and optimize resource utilization.

Therefore, the present study aims to compare the hematological response to daily versus twice-weekly oral iron supplementation among pregnant women with mild to moderate IDA. By focusing exclusively on hematologic parameters, the study seeks to generate evidence relevant to antenatal care in North Indian tertiary settings and inform national efforts under NIPI to refine iron supplementation strategies for pregnant women.

MATERIALS AND METHODS

Study Design and Setting: This was a prospective, randomized comparative study.

Study Setting: This study was conducted in the Department of Obstetrics and Gynaecology, Pt. B. D. Sharma Post Graduate Institute of Medical Sciences (PGIMS), Rohtak, Haryana.

Study Duration: The study was carried out for 14 months (February 2020 and March 2021)

Study Population: All pregnant women with mild to moderate iron deficiency anaemia coming to OPD at 14 -24 weeks of gestation.

Inclusion Criteria

- Pregnant women between 14–24 weeks gestation
- Singleton pregnancy
- Mild to moderate iron deficiency anaemia (haemoglobin 7–11 g/dL)
- Willing to participate and provide written consent

Exclusion Criteria

- Known intolerance to oral iron preparations
- Chronic systemic illness (renal, cardiac, hepatic disorders)
- Malabsorption syndromes
- Asymptomatic bacteriuria or active infection
- Multiple gestation
- Intrauterine fetal demise
- Pregnancy-induced hypertension or gestational diabetes
- Untreated thyroid disease

Sample Size Calculation: Sample size was calculated using the formula for comparing two means:

$$N = \frac{2SD^2(Z_1{-}_{\alpha/2} + Z_\beta)^2}{d^2}$$

Assumptions included:

- Standard deviation from previous studies: 0.55–0.64

- $Z_{1-\alpha/2} = 1.96$ (5% significance level)
- $Z_{\beta} = 0.842$ (80% power)
- Expected difference (effect size) based on mean haemoglobin change

The minimum sample size required was 64.78 per group, rounded to 100 participants per group for robustness, giving a total sample size of 200 women.

Methodology and Data Collection

Baseline Evaluation: At enrolment, each participant underwent a comprehensive clinical evaluation followed by baseline laboratory investigations. These included a complete blood count (CBC), haematocrit estimation, and peripheral blood smear to assess the type and severity of anaemia. Blood group and Rh typing were performed, along with screening for viral markers such as HIV, HBsAg, and HCV. Urine routine examination and culture were carried out to detect urinary tract infections, and thyroid function tests were conducted to rule out underlying endocrine disorders that could influence hematological status. In addition, all women received a single dose of Albendazole 400 mg for deworming as part of routine antenatal care to eliminate potential helminthic infestations contributing to iron deficiency.

Randomization and Intervention: Participants were randomized into two groups using a computer-generated random number sequence.

Group A (Daily Iron Supplementation, n = 100)

- One tablet daily containing 100 mg elemental iron (ferrous sulphate) + 500 mcg folic acid
- Issued three blister packs (10 tablets each) for 4 weeks

Group B (Twice-Weekly Iron Supplementation, n = 100)

- Two tablets containing 100 mg elemental iron + 500 mcg folic acid
- Taken twice weekly (Wednesday and Sunday)
- Issued two blister packs (10 tablets each) for 4 weeks

Both regimens were continued throughout the remainder of pregnancy.

Participants were followed at 4-weekly intervals until delivery, during which compliance with the assigned supplementation regimen was assessed through verification of empty blister packs and direct questioning regarding missed doses. At each follow-up visit, women were monitored for adverse effects commonly associated with oral iron therapy, including nausea, vomiting, constipation, diarrhea, epigastric discomfort, stool discoloration, and symptoms suggestive of persistent anemia. Clinical evaluation included a general physical and obstetric examination, while hematological monitoring involved repeat hemoglobin and hematocrit measurements along with peripheral blood smear review. These assessments, performed at enrolment and at each subsequent visit, enabled continuous evaluation of both tolerability and hematological response to the iron supplementation regimens.

Statistical Analysis: Data were collected using a structured proforma and entered into a computerized database. Quantitative variables (e.g., hemoglobin, hematocrit) were expressed as mean ±standard deviation (SD) and compared between groups using the unpaired t-test. Categorical variables (e.g., compliance, side effects) were presented as frequencies and percentages and analyzed using the Chi-square test. A p-value < 0.05 was considered statistically significant. Statistical analyses were conducted using SPSS version 21.0.

Ethical Approval: The study protocol was reviewed and approved by the Institutional Ethics Committee, PGIMS Rohtak. All participants were informed about the study objectives and procedures, and written informed consent was obtained prior to enrolment. Confidentiality was maintained throughout, and the study adhered to the principles of the Declaration of Helsinki.

RESULTS

A total of 234 pregnant women with mild to moderate iron deficiency anemia agreed to participate in the study, of whom 200 women meeting all eligibility criteria were randomized:
Group A (Daily iron) – 100 women
Group B (Twice-weekly iron) – 100 women
Both groups were comparable at baseline regarding age, parity, education, weight, and period of gestation at enrolment. Hematological parameters (hemoglobin and hematocrit) were also similar between the two groups at baseline.
At enrolment, both groups demonstrated comparable demographic and baseline hematological parameters. Mean hemoglobin levels indicated moderate anemia in both groups. No statistically significant differences were observed in any baseline characteristic.(Table 1)

Table 1: Baseline Demographic and Clinical Characteristics

Variable	Group A (n=100)	Group B (n=100)	p-value
Age (years), Mean ± SD	24.02 ± 3.86	23.31 ± 3.86	0.195
Parity, Mean	1.91	1.80	0.508
Gestational age at enrolment (weeks), Mean ± SD	18.39 ± 2.85	18.28 ± 2.61	0.776
Maternal weight (kg), Mean ± SD	57.15 ± 7.06	56.20 ± 7.59	0.361
Hb at enrolment (g/dL), Mean ± SD	8.59 ± 0.56	8.54 ± 0.59	0.507
Hematocrit at enrolment (%), Mean ± SD	31.45 ± 2.72	30.96 ± 2.49	0.186

Hemoglobin increased steadily in both groups during the antenatal period. The rise was slightly higher in Group A at early time points (4–16 weeks), while Group B showed a marginally higher value at 20 weeks. However, none of the differences reached statistical significance ($p > 0.05$). By 36 weeks and at delivery, both groups achieved similar hemoglobin levels.(Table 2)

Table 2: Comparison of Mean Hemoglobin (g/dL) at Follow-Up Visits

Time Point	Group A	Group B	p-value
At enrolment	8.59 ± 0.56	8.54 ± 0.59	0.507
After 4 weeks	9.01 ± 0.55	8.93 ± 0.57	0.305
After 8 weeks	9.48 ± 0.59	9.35 ± 0.56	0.112
After 12 weeks	9.80 ± 0.69	9.63 ± 0.55	0.072
After 16 weeks	10.13 ± 0.70	9.94 ± 0.57	0.102
After 20 weeks	10.10 ± 0.70	10.29 ± 0.55	0.358
At 36 weeks	10.15 ± 0.91	10.20 ± 0.54	0.684
At birth	10.14 ± 0.96	10.01 ± 0.65	0.255

Percentage improvement in hemoglobin showed a consistent upward trend across both groups. Group A exhibited a slightly greater percentage rise in early follow-up visits, though differences were not significant. By 36 weeks and at birth, both groups showed nearly identical improvement.(Table 3)

Table 3: Percentage Change in Hemoglobin Over Time

Time Interval	Group A (%)	Group B (%)	p-value
After 4 weeks	4.96 ± 2.62	4.65 ± 1.65	0.327
After 8 weeks	10.31 ± 5.15	9.63 ± 2.50	0.237
After 12 weeks	14.02 ± 8.05	12.90 ± 3.82	0.223
After 16 weeks	18.59 ± 8.99	16.17 ± 4.70	0.076
After 20 weeks	18.48 ± 7.18	17.73 ± 6.09	0.734
At 36 weeks	18.58 ± 11.82	18.58 ± 5.69	0.999
At birth	18.36 ± 12.25	17.52 ± 7.87	0.562

Hematocrit increased steadily in both groups. Differences between the daily and twice-weekly regimens remained statistically insignificant throughout the study period.(Table 4)

Table 4: Mean Hematocrit (%) at Follow-Up Visits

Time Point	Group A	Group B	p-value
At enrolment	31.45 ± 2.72	30.96 ± 2.49	0.186
After 4 weeks	32.73 ± 2.43	32.40 ± 2.54	0.349
After 8 weeks	34.34 ± 2.45	33.95 ± 2.40	0.254
After 12 weeks	35.89 ± 2.16	35.46 ± 2.18	0.171
After 16 weeks	37.04 ± 2.44	37.21 ± 2.04	0.687
After 20 weeks	38.32 ± 1.73	38.37 ± 1.80	0.927
After 36 weeks	37.72 ± 1.65	38.08 ± 2.05	0.219
At birth	37.32 ± 2.24	37.54 ± 2.19	0.484

Percentage change in hematocrit was similar between the two groups at most visits. A statistically significant difference was observed only at 16 weeks, where Group B showed a greater rise ($p = 0.013$). Beyond this point, both groups demonstrated comparable improvements.(Table 5)

Table 5: Percentage Change in Hematocrit Over Time

Time Point	Group A (%)	Group B (%)	p-value
After 4 weeks	4.22 ± 3.32	4.71 ± 2.96	0.270
After 8 weeks	9.37 ± 6.35	9.79 ± 3.42	0.566
After 12 weeks	14.06 ± 7.05	14.59 ± 4.38	0.533
After 16 weeks	16.74 ± 7.51	19.99 ± 5.75	**0.013**
After 20 weeks	20.43 ± 8.61	23.20 ± 6.30	0.265
At 36 weeks	20.80 ± 8.68	21.74 ± 6.95	0.441
At birth	19.29 ± 9.92	21.75 ± 8.75	0.065

DISCUSSION

Iron deficiency anaemia (IDA) continues to be one of the most significant public-health challenges globally and is particularly prevalent among pregnant women in low- and middle-income countries. WHO estimates that approximately 37% of pregnant women worldwide are anemic, with nearly half of these cases attributed to iron deficiency [1]. In India, the burden is even higher, with the National Family Health Survey (NFHS-5) reporting anaemia in 52.2% of pregnant women [6]. This high prevalence underscores the importance of effective iron supplementation strategies.

Oral iron supplementation remains the cornerstone of treatment for mild to moderate IDA in pregnancy due to its safety, affordability, and demonstrated efficacy in improving hematological markers [9]. Traditionally, daily iron supplementation has been recommended; however, emerging evidence suggests that intermittent iron therapy (once or twice weekly) may offer comparable hematological benefits with improved tolerability and adherence [13].

The present study evaluated the hematological response—specifically hemoglobin and hematocrit changes—to daily (100 mg elemental iron/day) versus twice-weekly (200 mg twice weekly) oral iron supplementation among pregnant women with mild to moderate IDA. Both groups were comparable at baseline in terms of demographic characteristics, parity, gestational age, and initial hematological indices, which allowed a fair comparison of the two regimens.

Effect of Daily vs. Intermittent Iron on Hemoglobin Levels

The baseline hemoglobin values in our study (8.59 g/dL in Group A and 8.54 g/dL in Group B) fell within the range of moderate anemia, consistent with national prevalence data [6]. A progressive increase in hemoglobin was observed in both groups across follow-up visits. Several previous trials also demonstrated comparable hemoglobin responses between daily and intermittent iron regimens.

A Cochrane systematic review by Peña-Rosas et al. reported no clinically significant difference in hemoglobin improvement between daily and intermittent supplementation during pregnancy [13]. Similarly, a randomized trial by Mukhopadhyay et al. in Indian women found equivalent rises in hemoglobin between daily and once-weekly iron therapy [16]. These findings align with our results, where no time point demonstrated a statistically significant difference in hemoglobin levels between the two groups.

The “mucosal block” hypothesis provides a physiological explanation for why intermittent dosing can yield similar results to daily dosing. Frequent iron intake upregulates hepcidin—a hepatic hormone that decreases intestinal iron absorption—reducing the absorption of subsequent doses given within 24–48 hours [11]. Intermittent supplementation, by allowing hepcidin levels to fall between doses, may therefore optimize fractional absorption. This mechanism is supported by controlled

metabolic studies showing higher iron absorption with alternate-day or intermittent dosing compared to consecutive daily supplementation [12].

Percentage Change in Hemoglobin

Both groups demonstrated comparable percentage increases in hemoglobin. Group A showed a slightly higher early rise, while Group B achieved similar improvements by later follow-up visits. These findings reinforce evidence that while daily dosing may produce a marginally faster initial response, long-term outcomes are equivalent, making intermittent dosing a feasible alternative.

Previous reports also indicate that intermittent dosing may be particularly advantageous in populations prone to poor adherence due to gastrointestinal side-effects. Tolkien et al. showed that daily iron is often associated with higher rates of nausea and constipation, contributing to poor compliance [10]. Although side-effects were not the primary focus of this paper, existing literature supports considering twice-weekly dosing to improve acceptability without compromising hematological outcomes.

Effect on Hematocrit

Hematocrit increased steadily in both groups throughout the antenatal period. Except for a single time point at 16 weeks where Group B showed a significantly greater percentage increase, all other comparisons were statistically similar. This finding is consistent with the physiology of iron absorption and erythropoiesis. Since hematocrit reflects red cell mass expansion over time, long-term trends tend to equalize when iron stores are replenished adequately, irrespective of dosing frequency. Studies by Stoffel et al. and Moretti et al. demonstrated that iron-deficient women may absorb lower daily doses more efficiently than higher doses, leading to comparable improvements in red-cell indices across dosing regimens [12,19]. Our results mirror these observations, reinforcing that both dosing schedules are effective in improving hematocrit in iron-deficient pregnant women.

Implications of Findings

The hematological response in our study demonstrates that twice-weekly iron supplementation is as effective as daily iron therapy in improving hemoglobin and hematocrit levels in pregnant women with mild to moderate IDA. This has several clinical and public-health implications:

1. Improved adherence: Intermittent dosing reduces pill burden and may enhance patient compliance, especially in resource-limited settings.
2. Reduced side-effects: Evidence shows intermittent dosing may reduce gastrointestinal intolerance, increasing acceptability [10].
3. Cost-effective: Using fewer tablets may reduce overall program costs, important for large-scale national programs such as the Iron Plus Initiative.
4. Physiological justification: Lower and less frequent dosing avoids hepcidin-mediated suppression of iron absorption, improving utilization [11,12].

Our findings align with global evidence demonstrating that intermittent oral iron is non-inferior to daily iron for improving hematological parameters in pregnancy [13,16,18]. WHO also endorses intermittent supplementation in settings where daily iron is not tolerated or adherence is poor [15]. Furthermore, the physiological basis for improved absorption with intermittent dosing has been validated in multiple recent absorption studies [12,19].

CONCLUSION

This prospective comparative study demonstrated that both daily and twice-weekly oral iron supplementation regimens are equally effective in improving hematological parameters among pregnant women with mild to moderate iron deficiency anaemia. Hemoglobin and hematocrit values increased steadily and comparably in both groups throughout pregnancy, with no statistically significant differences at most follow-up points. Although daily supplementation produced a slightly

faster initial rise, twice-weekly dosing achieved similar outcomes by later gestational ages, indicating non-inferiority. These findings support the physiological rationale for intermittent dosing, which may enhance iron absorption by reducing hepcidin-mediated suppression while also minimizing gastrointestinal side effects and improving adherence. Given the high burden of anaemia in Indian antenatal populations and the challenges of maintaining daily compliance, twice-weekly iron supplementation emerges as a practical, well-tolerated, and resource-efficient alternative without compromising hematologic efficacy. Adoption of flexible dosing strategies may therefore strengthen anaemia control efforts within national antenatal programs.

Declarations
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