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Original Article

Comparison of Effectiveness Cost Therapy and Increasing Level of Haemoglobin, Ferritin in Pregnant Women with Anemia Whom Are Given Iron Tablet Everyday and Every Two Days

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Abstract

Background : Anemia is common in pregnancy, with a prevalence of 48.9% in Indonesia (Riskesdas 2018). It increases the risk of impaired fetal growth, stunting, and intellectual disorders. Iron supplementation, as recommended by *Permenkes No. 88/2014*, is a key preventive strategy. Evidence such as Moretti et al. (2015), suggests that alternate-day supplementation improves absorption due to reduced hepcidin activity.
Aim : To evaluate the effectiveness of administering iron tablets every two days in terms of treatment cost, increases in hemoglobin (Hb) and ferritin levels, and incidence of gastrointestinal adverse effects.
Methods : This was a true experimental study using a randomized prepost test control group design. The control group received iron tablets daily for two months, while the intervention group received iron tablets every two days. The study was conducted at the Obstetrics and Gynecology Polyclinic of Kariadi Central General Hospital and Halmahera Primary Health Care over eight months (December 2023 – July 2024). Each group included 23 subjects. Body weight, hemoglobin, and ferritin were measured at baseline and after two months. Adverse effects and neonatal outcomes were also documented.
Results : Baseline characteristics were normally distributed. The intervention group showed a significant increase in hemoglobin and ferritin levels, higher neonatal birth weight, and lower treatment cost and adverse effects compared to the control group ($p < 0.05$). Post-treatment differences between groups were 0.5 g/dL for hemoglobin and 17.2 ng/mL for ferritin.
Conclusion : Administering iron tablets every two days is effective in improving hemoglobin and ferritin levels in pregnant women with anemia and is also cost-effective with fewer adverse effects.

Keywords : Anemia, Cost-effective therapy, Iron Supplementation, Pregnancy

INTRODUCTION

Anemia is a common complication during pregnancy and the postpartum period. Iron deficiency anemia (IDA) in pregnancy remains a major global health concern due to its significant impact on maternal and fetal outcomes. Anemia affects an estimated 36–40% of pregnant women, with iron deficiency recognized as the leading cause, accounting for approximately half of all cases worldwide.[1,2] The burden of iron deficiency anemia among pregnant women is particularly high in Southeast Asia, where prevalence rates consistently exceed the global average. Regional estimates indicate that more than 45–50% of pregnant women in Southeast Asia are affected by anemia, with some countries reporting prevalence above 60%.[1,3]

In Indonesia, the prevalence of anemia among pregnant women is 48.9%, with the highest proportion in women aged 15–24 years (Riskesdas 2018).[4] Anemia is defined as a reduction in hemoglobin (Hb), hematocrit, or red blood cell count. In pregnancy, anemia is diagnosed when Hb is <11 g/dL in the first and third trimesters or <10.5 g/dL in the second trimester.[5] Maternal anemia increases the risk of low birth weight, preterm birth, and impaired fetal neurodevelopment. In order to prevent and treat anaemia, pregnant women should take iron supplementation during pregnancy, puerperal period and breast feeding.[6]

Anemia during pregnancy may result from acute or chronic blood loss, increased red blood cell destruction, reduced production, or a combination of these factors. Iron deficiency remains the leading cause of decline red blood cells production. The total iron requirement during pregnancy reaches approximately 1000 mg to support maternal erythropoiesis, placental development, and fetal growth, as well as blood reserve to prepare for blood loss at delivery. Thus, universal iron supplementation is advised for all pregnant woman.[5,6]

According to WHO guidelines (2012), daily iron and folic acid supplementation reduces the risk of maternal anemia, iron deficiency, preterm delivery, and low birth weight.[7] Similarly, Indonesian regulation *Permenkes No. 88/2014* recommends daily iron–folic acid tablets for at least 90 days during pregnancy.[8] However, compliance is low, from 24% of women whom receive full course of 90 iron tablets recommended, only 38.1% of them take the 90 iron tablets as prescribed, indicating that the majority of pregnant women do not fully adhere to iron tablet intake.[4] Gastrointestinal side effects such as nausea, constipation, abdominal pain, and bloating, along with limited distribution of supplements throughout Indonesia, contribute to poor adherence pregnant women to take iron-folic acid regularly.[9]

Excess iron intake may also have negative effects, including oxidative stress, alterations of the gut microbiome, hypertensive disorders, small-for-gestational-age infants, and impaired placental blood flow.[10] These concerns support the use of intermittent regimens as a potentially safer alternative. Evidence shows that oral iron given every 48 hours improves absorption compared to daily dosing, with lower adverse effects. This is largely explained by hepcidin, a liver-derived hormone that regulates systemic iron levels, particularly their absorption. Hepcidin increases after oral iron administration and suppresses absorption for up to 24 hours, thereby reducing the benefit of daily dosing.[11]

Breymann *et al*. (2017) reported that daily oral iron supplementation at 100–200 mg/day for 28 days increases hemoglobin by approximately 0.61.3 g/dL.[11] By contrast, administration of ≥60 mg iron every 48 hours (alternate-day dosing) yields significantly greater fractional iron absorption than daily or twice-daily dosing, an effect mediated by transient increases in plasma hepcidin that suppress absorption for ≤24 hours after supplementation.[12] Alternate-day dosing therefore permits hepcidin to decline between doses, enhancing iron absorption and utilization.[12,13]

Hepcidin is a peptide hormone produced by the liver that functions as the principal regulator of systemic iron homeostasis. Hepcidin synthesis is modulated by circulating iron concentration and total body iron stores. Oral iron doses of 60–240 mg acutely increase hepcidin concentrations, which in turn reduce fractional iron absorption on the same day and the following day. Consequently, James *et al*. (2021) recommend administering iron supplementation every other day rather than daily to enhance iron absorption in pregnant women.[5] During pregnancy, hepcidin concentrations reach their nadir in the third trimester, facilitating maximal iron absorption and transfer to the maternal circulation in late gestation.[6]

In addition to regulating iron homeostasis in the maternal circulation, hepcidin also regulates the transfer of iron between the maternal and fetal compartments at the syncytiotrophoblast in the placenta. Maternal transferrin-bound iron is endocytosed by syncytiotrophoblasts and released in acidified endosomes; iron is then either stored in cytosolic ferritin or exported across the basolateral membrane into the fetal circulation via the iron exporter ferroportin. Hepcidin binds ferroportin, promoting its internalization and degradation, thereby modulating iron export to the fetal circulation.[13]

The standard oral iron supplementation dose ranges from 60–120 mg of elemental iron daily, whereas therapeutic doses for iron deficiency anemia typically range from 100–200 mg per day. Oral iron preparations are broadly classified into three categories: (1) iron salts, (2) iron polymaltose complexes, and (3) liposomal iron formulations. Among these, iron salts are the most commonly used in Indonesia for both supplementation

and treatment purposes. Ferrous sulfate, in particular, is widely utilized, especially in primary healthcare settings. Optimal absorption is achieved when iron is administered on an empty stomach, preferably in conjunction with an acidic beverage, such as citrus juice.[14]

Ferritin measurement is the most specific marker of iron deficiency, with values <30 µg/L indicating deficiency and <10–15 µg/L confirming iron-deficiency anemia either in pregnant or non-pregnant women. Another type of anaemia other than iron deficient may need further examination such as blood smear, haemoglobin electrophoresis, until bone marrow puncture (BMP).[5]

Based on this background, we conducted a study comparing daily versus alternate-day oral iron supplementation in pregnant women with anemia. Outcomes assessed included maternal Hb, ferritin, gastrointestinal side effects, neonatal birth weight, and also gestational age at delivery. A cost-effectiveness analysis was also performed to evaluate the economic impact of both regimens with CEA *(Cost Effectiveness Analysis)* method.[17]

METHODS

This study was a randomized, double-blind, placebo-controlled clinical trial using a prepost test control group design. The trial compared two regimens of oral iron therapy in pregnant women with anemia, and both interventions were administered for two months :

- Control group : daily oral iron supplementation.
- Intervention group : oral iron supplementation every two days.

The study was conducted at the Obstetric Polyclinic of Dr. Kariadi Hospital and the Mother and Child Polyclinic, Halmahera Primary Health Centre. The study, including recruitment, intervention, and follow-up, lasted for eight months.

Eligibility Criteria

Pregnant women with anemia (hemoglobin 7–10.9 g/dL) were recruited. Written informed consent was obtained from all participants prior to enrolment.

Inclusion criteria:

1. Gestational age 0–20 weeks or 28–32 weeks.
2. Normal pre-pregnancy Body Mass Index (BMI).
3. Mild anemia (Hb 10–10.9 g/dL) or moderate anemia (Hb 7–9.9 g/dL).

Exclusion criteria:

1. History of hematological disorders (e.g., hemolytic anemia, thalassemia, anemia due to chronic disease).
2. Liver or kidney disease.
3. Gastrointestinal disorders (e.g., acute gastritis, inflammatory bowel disease, post-bowel resection).
4. Allergy to ferrous sulfate, vitamin B complex, or vitamin C.

Randomization was performed using a computer-generated randomization table prepared by an independent pharmacist. Participants were assigned to either the control group (daily iron) or the intervention group (alternate-day iron).

Both participants and investigators were blinded to treatment allocation. Placebo tablets, identical in appearance to the active tablets, were used to ensure blinding.

In the beginning of the study, at baseline all participants underwent measurements of body weight, hemoglobin, and serum ferritin.

- Iron supplementation: ferrous fumarate (60 mg elemental iron) combined with folic acid (400 mcg).
- Placebo: tablets identical in appearance, without iron and folic acid.
- Additional supplements for both groups: vitamin C (250 mg daily) and vitamin B12 (50 mg daily) for two months.

Participants were counselled to reduce tea consumption and increase acidic food intake to optimize iron absorption. Tablets were dispensed monthly, and participants returned for follow-up and new supplies of medication.

- Primary outcomes: changes in hemoglobin and serum ferritin levels after two months.
- Secondary outcomes: born baby weight and gastrointestinal adverse effects.

Adverse effects were recorded using a Monitoring and Evaluation (MONEV) form, completed by participants at home and collected during follow-up visits.

Participants attended two follow-up visits:

1. At 1 month: collection of MONEV forms, dispensing of new supplements.
2. At 2 months: final assessment of hemoglobin, serum ferritin, and body weight. Participants also return their second MONEV forms in this visit.

After one month of supplementation with iron–folic acid, vitamin C, and vitamin B complex, all participants in each group were scheduled for a follow-up visit at either the Obstetrics Polyclinic of Kariadi Hospital or the Maternal and Child Health Polyclinic at Halmahera Primary Health Care. During these visits, participants received a subsequent supply of ferrous sulfate, vitamin B complex, and vitamin C. They were also required to submit their MONEV forms prior to undergoing routine antenatal assessments, including physical examination and ultrasonography. At the final follow-up visit, conducted two months after initiation of supplementation, all participants underwent repeat measurements of body weight, hemoglobin levels, and serum ferritin concentrations.

After those two months follow-up, pregnancy outcomes were subsequently monitored through telephone or direct messages until delivery. We followed the pregnancy progression of both groups via telephone

or messaging, with particular attention to participants' delivery outcomes. We documented the mode of delivery, neonatal birth weight, and the infant's general health condition at birth.

The sample size was calculated using a minimum sample size formula, resulting in 46 participants : 23 in the control group and 23 in the intervention group.

In this randomized, double-blind clinical trial, predefined dropout criteria were established prior to study initiation. Participants were considered eligible for withdrawal if they experienced serious adverse events related to the intervention, demonstrated non-compliance with the study protocol (including failure to adhere to supplementation or scheduled follow-up visits), developed medical conditions necessitating discontinuation, or were lost to follow-up despite repeated contact attempts. Participants were also informed that they had the right to withdraw or discontinue their participation at any time and at any phase of the study without any consequences.

During the study period, all participants were successfully followed through to completion in accordance with the study protocol. No participants met the predefined dropout criteria, and there were no instances of withdrawal or loss to follow-up. Consequently, all enrolled participants from both the control and intervention groups were included in the final analysis.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 27. Descriptive statistics were used to summarize baseline characteristics, with continuous variables presented as mean ± standard deviation. Normality was assessed using the Shapiro–Wilk test.

For within-group (intragroup) comparisons, changes before and after the intervention were analyzed using paired t-tests for normally distributed data. Whether for between-group (intergroup) comparisons between the control and intervention groups, independent t-tests were applied for normally distributed variables. Categorical variables were compared using the Pearson chi-square test as appropriate. A p-value of <0.05 was considered statistically significant in this study.

All participants were followed prospectively until delivery. Data were systematically collected for each participant, beginning with baseline (pretest) measurements at the initial visit and continuing through to maternal and neonatal outcomes after delivery. The total duration of the study was eight months, including the period required for data analysis.

RESULTS

Data were analyzed using SPSS version 22 for Microsoft. Normality was tested using the Shapiro–Wilk test, and homogeneity was tested using Levene's test. All five parameters demonstrated normal distribution and homogeneity, allowing the use of parametric tests. For within-group comparisons (pre vs post-therapy), the paired t-test was applied. For between-group comparisons (post-therapy outcomes), the independent t-test was used.

Table 2 shows that weight, hemoglobin (Hb), and ferritin increased significantly from pre- to post-therapy within each group. When comparing post-therapy results between groups, only Hb and ferritin showed significant differences, while weight did not. This suggests that iron supplementation every two days significantly improves Hb and ferritin levels, though not maternal weight.

To assess pregnancy outcomes, gestational age at delivery and birth weight were analyzed, while maternal outcomes focused on gastrointestinal side effects. In the treatment group, 23 infants were delivered (from 23 subjects), while in the control group, 20 infants were delivered (from 23 subjects).

From Table 3, birth weight differed significantly between groups, with infants in the treatment group weighing on average 292 g more than those in the control group (p=0.028). However, there was no significant difference in mean gestational age at delivery (p=0.085).

TABLE 1
Subject characteristic in both control and treatment group

Parameter	Control Group (Mean ± SD)	Treatment Group (Mean ± SD)	*p*-value
Age (years)	27.83 ± 4.93	26.57 ± 4.73	0.930
BMI before pregnancy (kg/m²)	23.75 ± 2.94	20.76 ± 2.65	0.758
Weight pre-therapy (kg)	58.89 ± 9.30	53.87 ± 8.50	0.959
Hemoglobin pre-therapy (g/dL)	9.40 ± 0.91	9.97 ± 0.71	0.178
Ferritin pre-therapy (ng/mL)	22.36 ± 4.76	22.90 ± 5.31	0.616

TABLE 2
Subject characteristic pre and post therapy in both groups

Parameter	Control Group (Mean ± SD)	Treatment Group (Mean ± SD)	*p*-value a	*p*-value b	*p*-value c
Weight (kg)	Pre: 58.89 ± 9.30	Pre: 53.87 ± 8.50	0.000	0.000	0.207
	Post: 60.47 ± 9.30	Post: 57.04 ± 8.79			
	Δ: +1.58	Δ: +3.17			
Hemoglobin (g/dL)	Pre: 9.40 ± 0.91	Pre: 9.97 ± 0.71	0.000	0.000	0.000
	Post: 10.45 ± 1.02	Post: 11.58 ± 0.62			
	Δ: +1.05	Δ: +1.61			
Ferritin (ng/mL)	Pre: 22.36 ± 4.76	Pre: 22.90 ± 5.31	0.003	0.004	0.000
	Post: 32.84 ± 12.59	Post: 50.60 ± 11.88			
	Δ: +10.48	Δ: +27.70			

TABLE 3
Born Baby Outcomes

Parameter	Control Group (Mean ± SD)	Treatment Group (Mean ± SD)	Δ (Difference)	*p*-value
Birth weight (g)	2637 ± 513.76	2929 ± 314.57	+292 g	0.028
Gestational age at delivery (weeks)	37.55 ± 1.39	38.22 ± 1.08	+0.67 weeks	0.085

These results indicate that iron supplementation every two days may improve birth weight but does not reduce the risk of preterm labor compared with daily supplementation.

Maternal Adverse Effects

Adverse gastrointestinal effects were monitored for two months using the MONEV (Monitoring and Evaluation) form. Adverse events were classified as:

1. No symptoms
2. Mild (disappeared without medication)
3. Moderate (disappeared with medication)
4. Severe (requiring hospitalization)

No severe adverse events were reported. In the treatment group, most subjects experienced no symptoms (19/23), and only 3/23 required medication. In contrast, the control group reported higher rates of gastrointestinal discomfort. Pearson's Chi-square analysis showed a significant difference between groups (p=0.000), indicating that gastrointestinal side effects were milder in the treatment group.

The increase in Hb and ferritin was further evaluated using the N-Gain formula (Figure 1), which measures improvement relative to an ideal value (Hb: 11 g/dL; Ferritin: 70 ng/mL). Table 5 shows significant prepost improvements for hemoglobin and ferritin in both groups. However, as shown in Table 7, daily iron supplementation was effective in raising Hb only, while alternate-day supplementation was effective in raising both Hb and ferritin significantly.

To facilitate interpretation of effectiveness, the N-gain percentage was subsequently categorized into predefined effectiveness levels. In this study, the effectiveness classification proposed by Richard R. Hake (1999) was applied, as presented in Tables 6 and 7.

As shown in Table 7, daily administration of oral iron was found to be less effective in increasing serum ferritin levels, although it remained effective in improving hemoglobin levels. In contrast, alternate-day (every two days) oral iron administration resulted in significant and effective increases in both serum ferritin and hemoglobin levels.

Furthermore, the comparison of changes in hemoglobin and ferritin levels before and after therapy in both groups is illustrated in Figure 2.

Economic evaluation was performed using the Average Cost-Effectiveness Ratio (ACER) and Incremental Cost-Effectiveness Ratio (ICER). ACER is defined as the ratio of total cost to effectiveness (ACER =

TABLE 4
Maternal side effects in control and treatment group

Group	No symptoms, n (%)	Disappeared without medication, n (%)	Disappeared with medication, n (%)	Total, n
Control	6 (26.1%)	10 (43.5%)	7 (30.4%)	23
Treatment	19 (82.6%)	1 (4.3%)	3 (13.0%)	23
Total	25 (54.3%)	11 (23.9%)	10 (21.7%)	46

Chi-square test: $p<0.001$, indicating a significant difference between groups

TABLE 5
N–Gain score for haemoglobin and ferritin

Parameter	Mean Difference (Treatment – Control)	95% CI for Mean Difference	*p*-value
N-Gain Ferritin (ng/mL)	17.23	23.29 to 11.18	<0.001
N-Gain Hemoglobin (g/dL)	0.56	0.82 to 0.31	<0.001

$$\text{N-Gain} = \frac{\text{Post Test score} - \text{Pre Test score}}{\text{Ideal value} - \text{Pre Test score}}$$

Figure 1. N-Gain Formula (Hake,R.R, 1999)

cost/effectiveness), where a lower value indicates greater cost-effectiveness.[18] ICER represents the additional cost per additional unit of effectiveness between two interventions and is calculated as (Cost_intervention − Cost_control) / (Effect_intervention − Effect_control).[18,19] A negative ICER indicates that the intervention is dominant (more effective and less costly).[19]

The treatment group (every two days) showed lower ACER values for Hb (31.50 vs 143.35) and ferritin (159.18 vs 838.64) compared with the control group. For ICER, alternate-day iron supplementation reduced costs by Rp 258 for every 1% increase in effectiveness in raising ferritin (17.2 ng/mL), and by Rp 57 for every 1% increase in effectiveness in raising Hb (0.5 g/dL). These findings indicate that iron supplementation every two days is more cost-effective than daily supplementation.

DISCUSSION

Anemia in pregnancy can impair fetal growth and development. Oral iron supplementation remains the primary strategy to correct anemia during pregnancy. Daily administration of oral iron has been proven to increase hemoglobin levels significantly. However, gastrointestinal adverse effects are common, often leading to reduced compliance and potentially hindering anemia improvement. To address this, several studies have proposed alternate-day or intermittent oral iron regimens as alternatives. This study compared the effectiveness, safety, and cost efficiency of daily versus alternate-day iron supplementation in pregnant women with anemia.

Recent RCTs in pregnant populations indicate that alternate-day iron supplementation achieves similar improvements in hemoglobin levels compared to daily regimens. A 2025 randomized controlled trial reported no significant difference in hemoglobin response between alternate-day and daily supplementation in pregnant women with iron deficiency anemia.[20] These findings are consistent with a 2024–2025 meta-analysis demonstrating that intermittent regimens produce comparable increases in hemoglobin and ferritin concentrations to daily supplementation.[10] Other studies, such as Chu Lam *et al*.[21] and Von Siebenthal *et al*.[22], also reported no significant differences between alternate-day and daily supplementation in improving hemoglobin and ferritin levels.

Conversely, some recent trials suggest a potential advantage of alternate-day dosing. A 2024 randomized study showed greater short-term hemoglobin increments

TABLE 6
Effectiveness Level Criteria

No	Percentage	Interpretation
1	< 40	Not Effective
2	40 – 55	Less Effective
3	56 – 75	Quite Effective
4	> 76	Effective

TABLE 7
N-Gain percent and interpretation

No	Parameter	Mean Percent Control (%)	Mean Percent Treatment (%)	Control Interpretation	Treatment Interpretation
1	N-Gain Percent Ferritin	22.85 + 25.7	60.02 + 24.85	Less Effective	**Quite Effective**
2	N-Gain Percent Haemoglobin	133.68 + 147.05	303.26 + 351.28	**Effective**	**Effective**

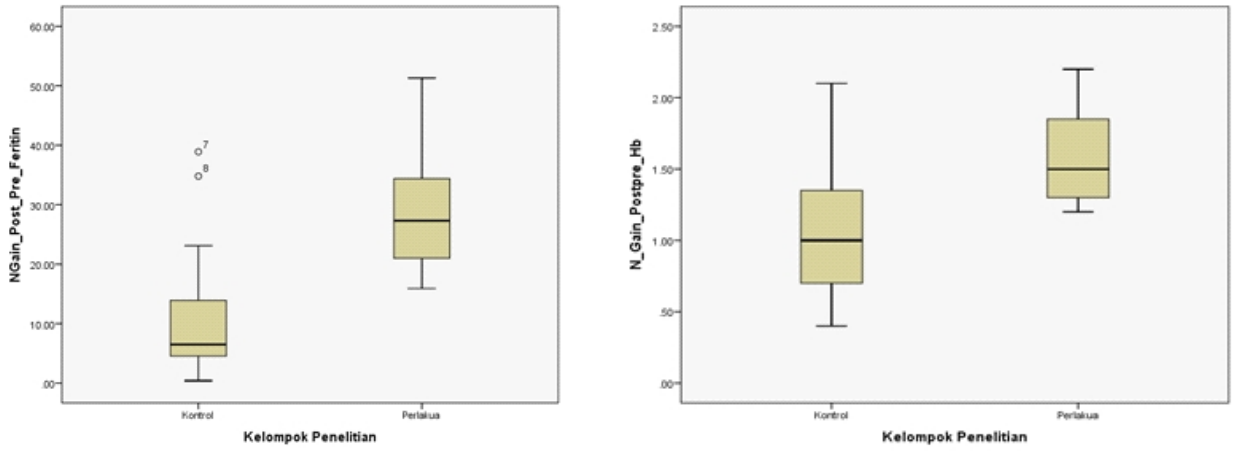

Figure 2. Histogram of N-Gain value before and after treatment

and fewer adverse effects in the alternate-day group.[23] Similarly, a 2025 clinical study reported more sustained improvement in both hemoglobin and iron stores (ferritin) with alternate-day supplementation.[24] However, these findings are not universal, and heterogeneity in study design, baseline anemia severity, and dosing regimens may explain discrepancies across studies. Overall, the current body of evidence supports a non-inferiority of intermittent dosing, with some studies suggesting superiority in specific contexts (e.g., moderate anemia or poor adherence populations).

Gastrointestinal side effects including nausea, constipation, and abdominal discomfort are common barriers to adherence in pregnant women receiving oral iron. Evidence from recent trials and meta-analyses indicates that intermittent regimens are associated with fewer adverse effects, which may improve compliance.[10] Improved adherence may, in turn, enhance overall effectiveness despite lower dosing frequency. However, not all RCTs demonstrate significant differences in side effect profiles. Some studies report similar tolerability and adherence between regimens, suggesting that patient-specific factors and iron formulation may also influence outcomes.[20]

In this study, baseline variables including maternal weight, hemoglobin, and ferritin were homogenous and normally distributed (p >0.05). Therefore, parametric tests were applied for analysis.

Paired t-tests were used to compare pre- and post-therapy changes within each group, while independent t-tests were used to evaluate differences between groups post-therapy.

Both groups showed significant increases in maternal weight, hemoglobin, and ferritin after two months of therapy. However, post-intervention comparison between groups revealed significant differences only in hemoglobin and ferritin, not in maternal weight gain. The alternate-day regimen increased hemoglobin and ferritin significantly, with N-gain analysis showing differences of 0.56 g/dL for hemoglobin and 17.23 ng/mL for ferritin compared with the daily regimen. These findings are consistent with the effectiveness interpretation criteria proposed by Hake[25], which indicated that alternate-day supplementation was effective for both hemoglobin and ferritin improvement, whereas daily supplementation was effective only for hemoglobin.

Maternal and neonatal outcomes were also assessed. Although the risk of preterm delivery was comparable between groups, infants born to mothers in the alternate-day group had a mean birth weight 292 grams higher than those in the daily group. In terms of tolerability, gastrointestinal side effects were milder in the alternate-day group, with only 3 of 23 pregnant women subjects requiring symptomatic treatment, compared to the daily group. These findings align with Karakoc *et al*.[26], who reported significantly lower rates of gastrointestinal side effects in alternate-day supplementation (15.7%) compared with daily supplementation (41.1%, $p = 0.0057$).

From a clinical perspective, these findings indicate that alternate-day iron supplementation represents a viable alternative to conventional daily dosing. This approach may be particularly beneficial for pregnant women who experience gastrointestinal intolerance, especially during the first trimester, when adherence to daily therapy is often compromised. Additionally, intermittent regimens may be advantageous in populations with poor adherence to daily supplementation, such as those in low- and middle-income countries, where limitations in medication supply and lower levels of health literacy may affect consistent intake. Furthermore, alternate-day dosing may be preferable in clinical settings where optimization of iron absorption efficiency is a priority.

Economic evaluation in this study further supported the alternate-day regimen. Cost-effectiveness analysis using ACER showed that alternate-day supplementation was more cost-effective for both hemoglobin (31.50 vs. 143.35) and ferritin (159.18 vs. 838.64). ICER analysis demonstrated that alternate-day therapy reduced costs by Rp 258 for every 17.2 ng/mL increase in ferritin and Rp 57 for every 0.5 g/dL increase in hemoglobin. These findings are supported by Taylor *et al*.[27], who showed that non-daily oral iron regimens offer comparable outcomes to daily regimens but with fewer adverse effects and lower treatment costs. To our knowledge, this is the first study in Indonesia to compare the cost-effectiveness of daily versus alternate-day oral iron supplementation in pregnant women.

CONCLUSION

This study demonstrated that alternate-day oral iron supplementation is comparable to daily supplementation in its effectiveness for increasing both hemoglobin and serum ferritin levels among pregnant women. Importantly, the alternate-day regimen was associated with several additional advantages, including a lower incidence of gastrointestinal side effects, which are commonly reported with daily iron intake and may negatively impact adherence. Improved tolerability may, therefore, contribute to better compliance with treatment protocols. Furthermore, the findings indicated a positive impact on neonatal outcomes, as reflected by improved birth weight among infants born to mothers in the alternate-day group. From an economic perspective, the reduced frequency of administration also translates into lower overall treatment costs, making this regimen particularly advantageous in resource-limited settings.

Taken together, these results suggest that alternate-day oral iron supplementation represents a practical and effective alternative to conventional daily dosing for the management of anemia during pregnancy. This approach may be especially beneficial in populations where treatment adherence and cost are significant challenges. Future studies with larger sample sizes and diverse populations are warranted to further validate these findings and support broader implementation in clinical practice.

CONFLICT OF INTEREST

The author declare no conflict of interest.

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REFERENCES

1. World Health Organization. *Global anaemia estimates, 2021 edition: anaemia in women and children*. Geneva: WHO; 2021
2. Stevens GA, Finucane MM, De-Regil LM, *et al*. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in pregnant and non-

pregnant women. *Lancet Glob Health*. 2013;1(1):e16–e25
3. Sunuwar DR, Singh DR, Chaudhary NK, *et al*. Prevalence and factors associated with anemia among women of reproductive age in South and Southeast Asian countries. *PLoS One. 2020*;15(8):e0236449
4. Badan Penelitian dan Pengembangan Kesehatan. Laporan Nasional RISKESDAS 2018. Jakarta: Kementerian Kesehatan RI; 2018.
5. James AH. Iron deficiency anemia in pregnancy. Obstet Gynecol. 2021 Oct;138(4):663–74.
6. Fisher AL, Nemeth E. Iron homeostasis during pregnancy. Am J Clin Nutr [Internet]. 2017; [cited 2025 Sep 11]. Available from: https://doi.org/10.3945/ajcn
7. World Health Organization. Guideline: Daily iron and folic acid supplementation in pregnant women [Internet]. Geneva: WHO; 2012 [cited 2025 Sep 11]. Available from: https://www.who.int
8. World Health Organization. Daily iron and folic acid supplementation in pregnant women: WHO Guideline 2012 [Internet]. 2012 [cited 2025 Sep 11]. Available from: https://peraturan.go.id
9. Bloor SR, Schutte R, Hobson AR. Oral iron supplementation––gastrointestinal side effects and the impact on the gut microbiota. Microbiol Res. 2021;12:491–502.
10. Banerjee A, Athalye S, Shingade P, Khargekar V, Mahajan N, Madkaikar M, *et al*. Efficacy of daily versus intermittent oral iron supplementation for prevention of anemia among pregnant women: a systematic review and meta-analysis. EClinicalMedicine. 2024 Aug;74:102221.
11. Breymann C, Auerbach M. Iron deficiency in gynecology and obstetrics: clinical implications and management [Internet]. 2019 [cited 2025 Sep 11]. Available from: https://www.myironfriend.com
12. Moretti D, Goede JS, Zeder C, Jiskra M, Chatzinakou V, Tjalsma H, *et al*. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. Blood [Internet]. 2015;126(17):1981–9. Available from: https://clinicaltrials.gov
13. Koenig MD, Tussing-Humphreys L, Day J, Cadwell B, Nemeth E. Hepcidin and iron homeostasis during pregnancy. Nutrients. 2014;6(8):3062–83.
14. Garzon S, Cacciato PM, Certelli C, Salvaggio C, Magliarditi M, Rizzo G. Iron deficiency anemia in pregnancy: novel approaches for an old problem. Oman Med J. 2020 Sep;35(5):e166.
15. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 233: Clinical management guidelines for obstetriciangynecologists. Obstet Gynecol. 2021 Aug;138(2):e55–64.
16. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin: Clinical management guidelines for obstetriciangynecologists. Obstet Gynecol. 2008 Jul;112(1):201–7.
17. Desianti S, Dan K, Lestari K. Kajian farmakoekonomi yang mendasari pemilihan pengobatan di Indonesia: review artikel. Jurnal Farmasi Klinik Indonesia. 2018;7(2):140–7.
18. Methods for the Economic Evaluation of Health Care Programmes. Report.
19. Yajamín-Villamarín R. The Importance of a Methodological Manual for Economic Evaluations in Healthcare Decision-Making in Ecuador. Pharmacoecon Open. 2025 Sep 1;9(5):713–22. https://doi.org/10.1007/s41669-025-00585-z
20. Lam MC, *et al*. Daily versus alternate-day iron supplementation for treatment of iron deficiency anemia in pregnancy: a randomized controlled trial. *Am J Perinatol*. 2025. (PubMed)
21. Chu Lam MT, Khandakar B, Heon I, Hussain FN, Feldman KM, Kaplowitz E, *et al*. Daily vs alternate day iron for pregnant women with iron deficiency anemia: randomized controlled trial. Am J Obstet Gynecol. 2021 Feb;224(2 Suppl):S107.
22. von Siebenthal HK, Gessler S, Vallelian F, Steinwendner J, Kuenzi UM, Moretti D, *et al*. Alternate day versus consecutive day oral iron supplementation in iron-depleted women: a randomized double-blind placebo-controlled study. EClinicalMedicine. 2023 Nov;65:102291.
23. Manivannan P, *et al*. Daily versus alternate-day oral iron replacement in iron deficiency anemia: randomized controlled trial. *Indian J Hematol Blood Transfus*. 2024. (ResearchGate)
24. Mawla MJ, *et al*. Alternate-day versus daily iron supplementation in women with iron deficiency anemia: a clinical study. *Iraqi Natl J Med*. 2025. (Iqnjm)
25. Hake RR. Analyzing change/gain scores. Unpublished [Internet]. 1999 [cited 2025 Sep 11]. Available from: http://www.physics.indiana.edu/~sdi/AnalyzingChange-Gain.pdf
26. Karakoc G, Orgul G, Sahin D, Yucel A. Is every other day iron supplementation effective for the treatment of iron deficiency anemia in pregnancy? J Matern Fetal Neonatal Med. 2022;35(5):832–6.
27. Taylor P, Jain A, Hadi A, Iansavitchene A, Lazo-Langner A. Daily versus non-daily oral iron supplementation for the treatment of iron deficiency anemia: a systematic review and meta-analysis of randomized trials. Blood [Internet]. 2024 Nov 5;144(Suppl 1):5261. Available from: https://ashpublications.org/blood/article/144/Supplement%201/5261/526801