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Intermittent Versus Regular Daily Regimen of Antenatal Oral Iron Supplementation for Preventing Iron Deficiency Anemia During Pregnancy

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ABSTRACT

Background: Anaemia is a medical condition that is quite frequent during pregnancy and the postpartum period globally. It poses several health hazards to both the mother and the child.

Objectives: This study aimed to evaluate the efficacy and adverse effects of intermittent versus regular daily regimen of antenatal oral iron supplementation for preventing iron deficiency anemia (IDA) during pregnancy.

Patients and methods: A prospective randomized controlled study was conducted at Departments of Obstetrics and Gynecology, Menoufia University Hospital and El Sahel Teaching Hospital through the period from February 2020 to December 2022. During this study, two hundred sixteen non-anemic pregnant women were enrolled and divided into 3 equal groups (each group included 72 patients): **Group A (daily)** received 60 mg of elemental iron + 1000 ug folic acid daily, **group B (every 3 days)** received 60 mg of elemental iron + 1000 ug folic acid twice weekly and **group C (once weekly)** received 120 mg of elemental iron + 2000 ug folic acid once weekly. Complete blood picture and serum ferritin were done at the start of the study and compared with follow up levels at 28 and 36 weeks.

Result: Demographic data were matched between groups. hemoglobin, hematocrit and ferritin levels before and after iron supplementation were comparable in the three groups regardless iron supplementation regimen. Iron side effects were more frequently encountered in group A than in groups B and C (27.8% vs 15.3% and 9.7% respectively). Regression analysis revealed that regimen of iron supplementation was not predictive of final hemoglobin concentration and the only significant predictor for final hemoglobin concentration was the initial hemoglobin level.

Conclusion: Intermittent (once or twice weekly) iron supplementation is advisable to non-anemic pregnant women as it is not associated with increased risk for developing anemia or ID when compared to daily regimen with fewer side effects.

Keywords: ID, Anemia, Iron Supplementation.

INTRODUCTION

Anaemia during pregnancy is characterised by a drop in hemoglobin < 11gm/dl or total RBCs, which results in a loss in the blood's ability to carry oxygen. Worldwide, anaemia is a very prevalent illness during pregnancy that has several health hazards for both the mother and the unborn child [(1)].

Generally non-specific, maternal signs and symptoms might include pallor, tiredness, dyspnea, palpitations, and dizziness. Anaemia has several well-known effects on mothers, such as increased risk of maternal death, decreased physical and mental function, decreased peripartum blood reserves, and higher risk of peripartum blood product transfusion [(2)].

Reduced red blood cell synthesis, increased red blood cell oxidation, or blood loss can all lead to anaemia. IDA is the most common cause of anaemia during pregnancy globally. Offspring of IDA-afflicted mothers are at a higher risk of low birth weight, preterm birth, infections, and even death during pregnancy. Studies based on observation reveal that iron shortage during pregnancy may cause distinct problems in the child's behaviour or cognitive development [(3)].

For a 55 kg woman, the average daily need for elemental iron during pregnancy is between 30 and 60 mg. Foetal development, placental requirements, and the rise in red cell mass are all supported by this iron. Up to 90% of women have iron reserves insufficient to fulfil the increased iron requirements throughout pregnancy and the postpartum period, and around 40% of women have low or no iron stores at the beginning of their pregnancy [(4)].

For non-anemic pregnant women in communities where the prevalence of anaemia is less than 20%, the WHO suggests an intermittent regimen (e.g., weekly 120 mg of elemental iron and 2.8 mg folate) as an effective substitute for a daily regimen for the prevention of anaemia during pregnancy. Oral supplements given once a week would expose new intestinal epithelial cells to each subsequent dose, improving iron absorption. It is believed that an oral dose of iron can become saturated in an intestinal epithelial cell, leading to decreased iron absorption because intestinal cell turnover happens every five to six days. Studies on weekly supplements have demonstrated comparable effects on mothers as those on daily supplements [(5)]. Moreover, intermittent oral iron supplementation may lessen the oxidative stress caused by free radicals, which harms the intestinal mucosa and causes the unfavourable gastrointestinal side effects linked to daily oral iron supplements. Consequently, weekly schedules could be more palatable to women, leading to higher levels of compliance [(6)].

However, it has been demonstrated that occasional supplementing programs raise the risk of

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mild anaemia in the long run, particularly in areas where anaemia and ID are very common. Moreover, while prenatal oral iron supplementation programs are successful. Additional techniques may be needed to enhance compliance, since the mere decrease of gastrointestinal side effects may not be sufficient [7].

A research conducted in 2001 showed that daily oral iron supplementation during pregnancy was much more effective in avoiding anaemia during the third trimester than weekly or thrice weekly regimens. The high frequency of anaemia and ID among the women arriving to the unit for prenatal care at that time likely contributed to this finding [8]. So, this study aimed to evaluate the efficacy and adverse effects of intermittent versus regular daily regimen of antenatal oral iron supplementation for preventing IDA during pregnancy.

PATIENTS AND METHODS

A prospective randomized controlled study was conducted at Obstetrics and Gynecology Departments, Menoufia University Hospital and El Sahel Teaching Hospital through the period from February 2020 to December 2022.

Inclusion criteria: Non-anemic pregnant women at any age group, Hb level ≥11 g/dl, single viable fetus and gestational age 12-20 weeks.

Exclusion criteria: women with haematological illnesses or chronic diseases (such as thalassemia, rheumatoid arthritis, or chronic renal disease) who are anaemic during pregnancy regardless of their haemoglobin level**,** multifetal pregnancy and women who had chronic blood loss e.g.: antepartum hemorrhage , threatened abortion, bleeding piles.

Method of randomization: Women who met the requirements for participation were randomised to either group. The 216 opaque envelopes have sequential numbers on them. A matching letter representing the assigned group was placed in each envelope in accordance with the randomization table. Next, each envelope was sealed and placed within a single box. Using MedCalc ® version 13, a computer-generated randomization sheet was used for the randomization process.

Sample size calculation: The sample size was calculated assuming a 22% difference in nausea as a side effect between the daily, weekly, and intermittent groups. In order to detect this difference with a significance level of 5%, 68 people per group are expected to be needed to reach 80% power. A total of 72 patients each group, with a 10% withdrawal/dropout rate, results in a sample size of 216 people overall.

Two hundred sixteen pregnant women were recruited and divided into 3 equal groups (each group included 72 patients): **Group A** received 60 mg of elemental iron + 1000 ug folic acid daily [2 capsules of Ferrofol (Epico)] daily after lunch. **Group B** received 60 mg of elemental iron + 1000 ug folic acid twice weekly [2 capsules of Ferrofol (Epico)] after lunch every 3 days. **Group C:** received 120 mg of elemental iron + 2000 ug Folic acid once weekly [4 capsules of ferrofol (Epico)] after lunch, as shown in **(Figure 1)**.

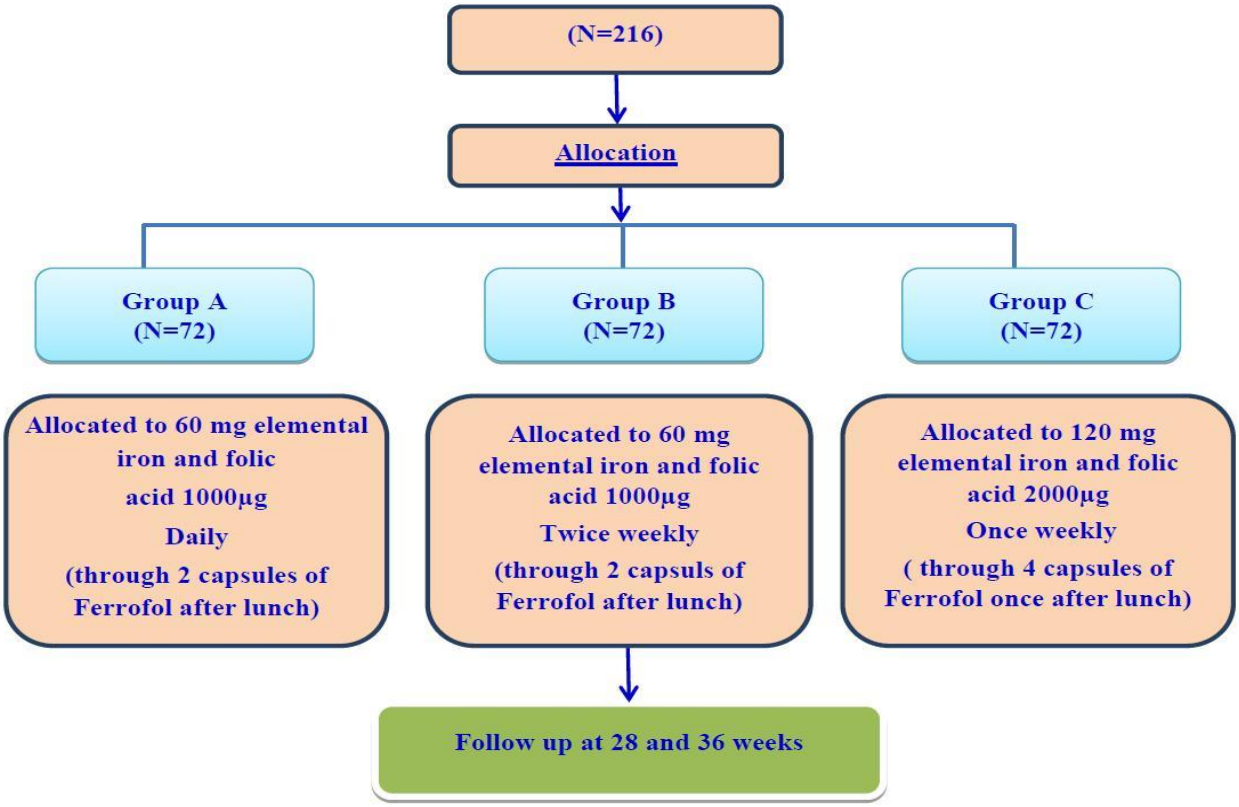

Figure (1): The CONSORT flow chart

Participants underwent complete history taking and general examination including weight, height, pallor and heart rate to establish the type/pattern of anemia and the presence of associated abnormalities such as renal and bone marrow problems, or signs of systemic illness and whether anemia is related to an underlying endocrine abnormality. **Ultrasound examination** was done by an expert sonographer.

Laboratory follow up: complete blood picture and serum ferritin were done at the start of the study for documentation and compared to follow up levels. Laboratory follow up by complete blood picture and serum ferritin were done again at 28 and 36 weeks. Side effects of the medication and convenience of continuation of iron in the three regimens were reported every 4 weeks.

Primary outcome: Effectiveness of iron therapy.

Secondary outcomes: Frequency of iron side effects mainly nausea, vomiting and constipation and neonatal outcomes.

Ethical approval: The Ethics Committee of Faculty of Medicine, Menoufia University granted the study approval. All participants signed informed consents after a thorough explanation of the goals of the study. The Helsinki Declaration was followed throughout the study's conduct.

Statistical Analysis:
An IBM PC running SPSS version 20.0 was used to gather, tabulate, and statistically analyse the data. Numbers and percentages for qualitative data and the mean, standard deviation (SD) and range and for quantitative data. Analytical statistics were employed to determine if the targeted disease and the factors under investigation are related. The Chi-square test (χ^2) was employed to investigate the relationship between two qualitative variables. The three groups with normal distributions and quantitative variables were compared using the ANOVA test of significance. A nonparametric test of significance called the Kruskall Wallis test was used to compare three groups with quantitative variables that are not regularly distributed. A significant p-value was ≤ 0.05.

RESULTS
As regards demographic data and general patient characteristics, there were no significant differences between the three groups (Table 1).

Table (1): Demographic characteristics of the studied groups (N=216)

Studied variables	Group A (N=72)	Group B (N=72)	Group C (N=72)	K	P value
Age / years					
Mean ±SD	24.6±3.19	25.5±4.16	26.1±4.97	3.75	0.153
Median	24.0	25.0	25.0		
Range	18.0 – 35.0	17.0 – 37.0	18.0 – 40.0		
Educational level					
Primary	2(2.80)	3(4.20)	2(2.80)	X^2	
Secondary	15(20.8)	20(27.8)	18(25.0)	2.16	0.904
University	35(48.6)	28(38.9)	29(40.3)		
Higher	20(27.8)	21(29.1)	23(31.9)		
Residence					
Rural	0(0.00)	0(0.00)	0(0.00)	-	-
Urban	72(100)	72(100)	72(100)		
Income				X^2	
Enough	40(55.6)	37(51.4)	33(45.8)	1.37	0.503
Not enough	32(44.4)	35(48.6)	39(54.2)		

K: Kruskall Wallis test.

There were no significant differences between groups regarding their hemoglobin, hematocrit and ferritin levels before and after iron supplementation (Table 2).

Table (2): Hemoglobin, hematocrit and ferritin levels before and after iron supplementation among the studied groups (N=216)

	Group A (N=72)	Group B (N=72)	Group C (N=72)	K	P value
Hemoglobin level					
Before supplementation Mean ±SD	11.8±0.26	11.8±0.37	11.7±0.21	5.18	0.075
At 28 weeks Mean ±SD	11.7±0.24	11.7±0.59	11.6±0.20	4.48	0.106
At 36 weeks Mean ±SD	11.6±0.22	11.5±0.51	11.5±0.24	3.24	0.445
Hematocrit level					
Before supplementation Mean ±SD	34.3±0.75	34.4±1.25	34.0±0.61	5.49	0.064
At 28 weeks Mean ±SD	34.6±0.70	34.6±0.85	34.3±0.62	4.93	0.085
At 36 weeks Mean ±SD	34.7±0.75	34.5±1.05	34.4±0.58	4.52	0.104
Ferritin level					
Before supplementation Mean ±SD	45.0±1.47	45.3±1.71	45.5±1.37	4.05	0.132
At 28 weeks Mean ±SD	34.8±0.82	34.5±1.00	34.6±1.53	2.38	0.303
At 36 weeks Mean ±SD	32.7±0.77	32.8±1.64	32.8±1.46	4.32	0.115

K: Kruskall Wallis test.

Regarding side effects of iron supplementation among the studied groups**,** nausea was significantly presented in group A than in groups B and C (27.8% vs 15.3% and 9.7% respectively, P value 0.014). Vomiting was significantly reported in group A than in groups B and C (18.1% vs 7% and 5.6%v respectively, P value 0.024). There was no discernible difference in constipation across the studied groups (P value 0.153) (Table 3).

Table (3): Side effects of iron supplementation among the studied groups (N=216).

Studied variables	Group A (N=72)		Group B (N=72)		Group C (N=72)		χ^2	P value
	No.	%	No.	%	No.	%		
Nausea								
Yes	20	27.8	11	15.3	7	9.70	8.49	**0.014***
No	52	72.2	61	84.7	65	90.3		
Vomiting								
Yes	13	18.1	5	7.00	4	5.60	7.39	**0.024***
No	59	81.9	67	93.0	68	94.4		
Constipation								
Yes	11	15.3	7	9.70	4	5.60	3.75	0.153
No	61	84.7	65	90.3	68	94.4		
Others								
Dyspepsia	1	1.40	2	2.80	1	1.40		
Heart burn	8	11.1	6	8.30	3	4.20	5.04	0.539
Metallic taste	4	5.60	3	4.20	1	1.40		
No	59	81.9	61	84.7	67	93.1		

*significant.

There were no significant differences between the studied groups regarding neonatal outcomes (preterm labour, Apgar scores and NICU admission) **(Table 4).**

Table (4): Neonatal outcomes among the studied groups (N=216)

Studied variables	Group A (N=72)	Group B (N=72)	Group C (N=72)	Test of sig.	P value
Preterm birth	10(13.9)	12(16.7)	11(15.3)	χ^2 0.215	0.898
Apgar at 1min Mean ±SD	5.51±0.50	5.47±0.50	5.41±0.49	K 1.37	0.504
Apgar at 5min Mean ±SD	7.44±0.50	7.44±0.50	7.34±0.47	K 1.86	0.394
NICU admission					
Yes	0(0.00)	0(0.00)	0(0.00)		
No	72(100)	72(100)	72(100)	-	-
Neonatal death					
Yes	0(0.00)	0(0.00)	0(0.00)		
No	72(100)	72(100)	72(100)	-	-
Neonatal weight Mean ±SD	2797.2±243.7	2798.6±237.0	2773.4±492.3	K 1.72	0.422

K: Kruskall Wallis test.

Regression analysis for the effect of initial Hb level, regimen of iron supplementation, age, gestational age and parity on final hemoglobin concentration revealed that regimen of iron supplementation was not predictive of final hemoglobin concentration and the only significant predictor for final hemoglobin concentration was the initial hemoglobin level (Table 5).

Table (5): Regression analysis for the effect of initial Hb, regimen of iron supplementation, age, gestational age, and parity on final hemoglobin level

	Coefficient	SE	P value
Maternal age	-0.001	0.007	0.873
Gestational age	-0.012	0.010	0.804
Daily iron regimen	-0.008	0.030	0.246
Intermittent iron Regimen	-0.005	0.032	0.453
Parity	0.028	0.026	0.286
Initial Hb level	0.170	0.083	**0.042***

Adjusted $R^2 = 0.009$ SEE = 0.351

DISCUSSION

Due to the increased iron needs during pregnancy, pregnant women are more vulnerable to anaemia [9]. The most sensible short-term solution to the issue is to make iron supplementation programs more successful [10]. The primary risks associated with regular iron supplementation include a high rate of unwanted side effects that result in low compliance. Gastrointestinal intolerance is a result of high iron dosages, which may have a harmful effect on the gut mucosa through iron-related oxidative stress [11]. Consequently, this prospective randomized controlled study aimed to ascertain if weekly prenatal oral iron and folate supplementation is a more effective way to prevent IDA during pregnancy than a daily regimen.

In our study, hemoglobin, hematocrit and ferritin levels before and after iron supplementation were comparable in the three groups regardless iron supplementation regimen. Also, as regards regression analysis initial hemoglobin level was the only independent predictor for final hemoglobin concentration (compared to regimen of iron supplementation, maternal age, gestational age and parity). **Peña-Rosas *et al.*** [12] assessed the advantages and disadvantages of giving pregnant women sporadic iron supplements, either on their own or in conjunction with folic acid or other vitamins and minerals, with regard to the outcomes of pregnancy and the newborn. They concurred with us and found that intermittent regimens led to comparable outcomes for mothers and babies as daily supplementing, with fewer adverse effects. However, there was a short-term rise in the risk of moderate anaemia. **Sadighian *et al.*** [13] compared the amount of iron supplements given to healthy expectant mothers on a daily and sporadic basis. They found that giving pregnant women an iron supplement on a daily or sporadic basis produced the same results. When it comes to iron side effects during pregnancy, a sporadic approach appears to be better than a daily one. **Bouzari *et al.*** [14] study examined the impact of daily, weekly, and three-time weekly iron supplementation on avoiding anaemia in healthy expectant mothers. They proposed that for healthy pregnant women without anaemia, iron supplementation three times a week or once a week is just as beneficial as daily supplementation.

Our results are also consistent with other earlier studies that found that weekly prescriptions of 120 mg elemental iron vs daily prescriptions of 60 mg elemental iron were equally beneficial in avoiding anaemia during pregnancy [15, 16]. Against our observations, **Casanueva *et al.*** [7] reported that greater final haemoglobin concentration was linked to daily iron delivery in a study of 21 published and unpublished trials comparing intermittent versus daily iron administration. Furthermore, our study's findings contradict those of prior research that examined how intermittent iron supplementation during pregnancy either raised or decreased the amount of haemoglobin, which is the marker for anaemia defined as Hb < 110g/L [17, 18]. On the contrary of our findings, Goonewarden ***et al.*** [19] examined the effects of prescription of 100 mg elemental iron three times a week, daily, and weekly. Serum ferritin, hematocrit, and haemoglobin levels were evaluated before and after the intervention. The results showed that weekly and three-times-weekly iron supplementation significantly increased the chance of developing IDA compared to a daily regimen. Pregnant women in IDA-risk neighbourhoods were advised to take an oral iron supplement every day.

As regards iron side effects in our setting, nausea and vomiting were significantly presented in group A (daily iron) compared to other groups. On the other hand, no significant differences were noted between the studied groups regarding constipation, dyspepsia, heart burn and metallic taste. **Mansour and Mohammed** [20] compared the haemoglobin levels in pregnant women who are not anaemic and are given iron supplements weekly as opposed to daily. They concurred with us and found that weekly iron supplementation, when used as a preventive measure in pregnant women who are not anaemic, is just as effective as daily supplementation in terms of the haemoglobin level and is linked to notably fewer adverse effects and more compliance. In agreement with our study **Lachili *et al.*** [21] observed a noteworthy rise in the frequency of gastrointestinal adverse effects associated with iron supplementation, including heartburn, nausea, constipation, and metallic taste. Gastrointestinal intolerance is a result of high iron dosages, which may have harmful consequences on the gut mucosa that are mediated by oxidative stress

associated to iron. High iron dosages are also linked to decreased absorption of other elements like zinc.

The impact of weekly vs daily iron supplementation on haematological and pregnancy outcomes was examined by **Mukhopadhyay *et al.*** [(22)]. For prophylactic purposes, weekly doses are just as effective as daily ones in terms of haemoglobin increase and perinatal outcome. Actually, patients reported much less adverse effects and were happier and more willing to follow the weekly routine. Serum ferritin levels were lower in the weekly supplemented group than in the daily group, suggesting that daily supplementation is preferable to weekly supplementation in anaemic women, even those with moderate anaemia. **Khangura *et al.*** [(23)] evaluated the haematological response of expectant mothers receiving daily vs intermittent iron therapy, as well as the evaluation of gastrointestinal adverse effects and treatment compliance. They concurred with us and stated that daily therapy was not inferior to intermittent iron therapy. Compared to the intermittent group, women in the daily group had greater nausea. The women in the sporadic group did not adhere to therapy any more.

Finally, our findings demonstrated that there was no statistically significant difference in newborn outcomes (NICU admission, Apgar scores, and preterm delivery) between the groups under study. Against us, a prior study by **Scholl and Reilly** [(24)] demonstrated that anaemia during pregnancy raises the chance of low birth weight and/or early delivery.

STRENGTH POINTS

There were no patients lost throughout the trial period, and the design of the study was prospective randomised controlled. In order to avoid IDA in pregnant women who are not anaemic, this research was the first at Menoufia University Hospitals to examine if weekly oral iron and folate supplements during pregnancy are a useful substitute for daily regimens. To the best of our knowledge, there are few studies in literature assessing our study outcomes and most of studies that disagreed with our results were due to different study methodology & sample size or different gestational age of studied cases at time of enrollment. Every attempt was made to ensure that all follow-up data were recorded and that the data analysis contained only full information. The same team conducted all clinical assessments and evaluated trial results.

LIMITATIONS

Because this study was hospital-based rather than multicentric, there were fewer cases and a lower sample size in relation to the study's findings.

CONCLUSION

We concluded that intermittent (once or twice weekly) administration of iron supplements is advisable to non-anemic pregnant women as it is not associated with increased risk for developing anemia or ID when compared to daily regimen with fewer side effects.

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