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Research Article

Iron Therapy

Effect of daily versus intermittent iron therapy in pregnant women: hematological and pregnancy outcome

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Background: The purpose of this study was to compare daily iron supplementation and intermittent iron supplementation in preventing anemia in healthy pregnant women. **Material and Method:** Prospective Randomized Clinical Trial. From May 2004 – December 2006, 141 healthy pregnant women without anemia, between 14 - 20 weeks of pregnancy were randomly allocated into two equal groups. Completed data were obtained in 110 patients, 55 in each group. The first group (n = 55) received a 100 mg-ferrous sulfate tablet daily, the second group (n = 55) received a 100 mg-ferrous sulfate tablet two tablets once weekly, respectively till delivery. Serum hemoglobin, ferritin, and iron were measured before and after the supplementation. Paired t and ANOVA tests were used as appropriate. **Results:** There were no significant differences between the pre- and post-treatment hemoglobin levels (p= 0.871) and serum ferritin levels (p= 0.741) with iron supplementation in the two groups when the maternal hemoglobin level was >11g/dL before enrolment. However, For those women who had a hemoglobin concentration <11gm/dL at the beginning, the rise in hemoglobin concentration was significantly greater at the end in the daily supplemented group as compared to the weekly group (1.44±1.51 gm/dl vs. 0.12±1.05 gm/dl, p=0.015). Although when the changes in the serum ferritin level which occurred in each group were compared, there was no significant difference (p=0.415) between the two intervention groups. **Conclusions:** These results suggest, daily or weekly iron supplementation is equally effective for healthy pregnant women without anemia.

Keywords: Iron supplementation, Pregnant women, Anaemia

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Background

Iron requirements increase during pregnancy [1,2]. And this requirement may lead to anemia in pregnant women [3,4]. Lower hemoglobin cut off is 11.0 g/dL in the first and last trimester and 10.5 g/dL in the second trimester. Therefore, any level below 10.5 g/dL should be considered as anemia [5]. Iron consumption for pregnant women is undesirable, because of the side effects. The probable cause is the effect of oxidative stress of high doses of Iron, which leads to gastrointestinal intolerance [3].

As gut mucosal turnover rates are about three days, administering iron during these days may lead to lower iron absorption. Periodic iron supplementation may let the mucosa to heal and gets better iron absorption [6-8]. Previous studies reported, continuous administration of oral iron impairs the absorption of a subsequent iron dose [9]. A few experimental studies demonstrated that alternative efficacious iron supplementation regimens might reduce undesirable side-effects [10].

Significant equality and reduced side effects have been reported in several epidemiological studies in comparing the weekly prescription of iron with daily supplementation [3-7]. In the other studies, there was not found a difference between daily and twice-weekly iron supplementation regimens in preventing iron deficiency anemia in children, non-pregnant women, and pregnant women in their early trimesters [12-14]. And in another study, the intermittent regimen was shown to be superior to daily regimen [3-15]. In human beings, gut mucosal turnover occurs every 3 days.

Thus, weekly rather than daily administration of iron has been proposed as a safe, beneficent, and cost-effective method to prevent and alleviate anemia in pregnant women [12-17]. As mentioned above there are different study which studied the effect of iron separately in daily use and weekly and three times. Thus authors aimed to compare the effects of daily and weekly iron supplementation regimens on hematological markers in pregnant women without anemia.

Methods

Setting: Department of Obstetrics and Gynecology, PBM Medical College, Bikaner, Rajasthan, India.

Duration of study: May 2004 to December 2006

Type of study: Prospective simply randomized clinical trial

Sampling methods: Unstratified variable block size random allocation

Sample size calculation: Sample size calculation was carried out. A sample size of 54 in each group would have 90% power to detect a difference in a mean of 2 g/dL in hemoglobin (the difference between the anticipated daily supplementation mean of 12 g/dL and the weekly supplementation mean of 10 g/dL) assuming the common standard deviation of 3.5 using a two-way t-test with a 0.05 one-sided significance level. Therefore, we planned to include 55 subjects in each arm of the study. Block randomization (block size = 10) was used as a method of allocating the subjects into one of two groups: one receiving daily and the other receiving weekly iron supplementation.

Inclusion criteria: All the pregnant women who attended the antenatal clinics before the 20th week of gestation were included in the study.

Exclusion criteria: Women with hemoglobin levels less than 10 g/dL, chronic hematological disorders (thalassemia, etc.), history of chronic illness e.g. liver or renal disease, recurrent urinary tract infection (UTI), tuberculosis, malaria, heart disease; the history of menorrhagia, bleeding disorders, chronic peptic ulcer, bleeding piles; women taking drugs e.g. antiepileptics, NSAIDs, antithyroid; the history of prior blood transfusion; obstetric hemorrhage is present or past pregnancies and multiple pregnancies were excluded from the study.

Data collection procedure: Hundred forty-one pregnant women without exclusion criteria were enrolled in the study between 14th to 20 weeks of gestation. Written informed consent was obtained from all the participants. The Ethics Committee of the hospital approved the study protocol. The women were divided into two equal groups. All the groups were matched in terms of age, numbers of pregnant, income, and education. Standard Govt. of India supply of Irofol (large) tablets was used throughout the study. Each tablet contains dried ferrous sulfate IP 335 mg equivalent to 100 mg of elemental ferrous iron and folic acid 500 µg.

Women in group I (n=55) were instructed to take one tablet daily and supplied 3 blister packets (total of 30 tablets) for 1 month. Women in group II (n=55) were supplied one blister packet (10 tablets) to cover one month. They were instructed to choose

Any day of the week and take two tablets on that day – one before lunch and the other before dinner (total 200 mg elemental iron/week). No tablets were given for the rest of the week and the regimen was repeated weekly. All women were instructed to take their iron tablets before their meals (30 minutes approx.) and not to take them with tea, coffee, or milk. They were advised to take calcium supplements after meals. Health education regarding the importance of diet in pregnancy, iron-rich food appropriate dietary practices was given to all.

Patients were advised to bring back their blister packets at each ANC visit. The number of days for which the drugs were consumed was recorded. An attempt was made to verbally verify compliance, and by checking the used blister packets. Patients were informed about the usual side effect of iron preparations and told to report nausea, vomiting, bowel disturbances, or any other complications. They were also to report if severe intolerance caused them to stop taking supplements. Serum hemoglobin, serum ferritin, and serum iron levels were measured for all pregnant women who attended the antenatal clinics before the 20th week of gestation.

A complete hemogram was repeated at 1 month and 3 months after starting supplementation. Final hemogram and serum ferritin estimation were done at 32-34 weeks period of gestation.

All women were followed till term. They continued to take iron supplements until delivery. The total number of tablets consumed in pregnancy, the period of gestation at delivery, and birth weight were noted.

Ethical consideration: The Ethics Committee of the hospital approved the study protocol

Table-1: Reason for attrition.

Reason	No. of patients		
	Total	Daily	Weekly
Refused further blood sampling	2	1	1
Changed residence	1	0	1
Miscarriage	3	2	1
IUD	2	2	0
APH – abruption – 1, previa – 1	2	2	0
Preterm	2	0	0
Lost to follow up	8	6	2
Changed iron preparation	9	7	2
Therapy discontinued	2	1	1
	31	21	10

Statistical analysis- Data on all subjects were entered into a computer database and analysis was performed using SPSS 18 advanced statistics program. All hematological variables fitted into normal distribution and parametric analysis using mean, standard error of mean and standard deviation were employed. The significance of the difference between the daily and weekly supplemented groups was assessed by the student's t-test for unpaired values and the chi-square test for non-parametric variables. Correlations were calculated using Pearson's coefficient of correlation.

The significance level was set at $p<0.05$. The main outcome measurements were a comparison of mean hemoglobin and ferritin levels, at the beginning and end of the supplementation period between the two treatment groups (between-subjects factor) as well as a comparison of the change within each group (within-subject factor). These treatment effects were compared by using analysis of variance (ANOVA). Kaplan-Meier analysis was performed to determine whether there was a significant difference in the probability of improvement relative to the time in the two groups.

Results

One hundred and forty-one women were initially enrolled in the study. Completed data were obtained in 110 patients – 55 in the daily supplemented group and 55 in the weekly supplemented group. The reasons for attrition are shown in Table 1. Reasons which were common to both groups included: 2 women refused a second blood collection; 1 woman changed residence and 8 women were lost to follow up. Nine women had miscarriage/delivery before 32 weeks gestation and were excluded because the final ferritin level could not be done.

More women (n=7) complained of severe GI intolerance in the daily group as compared to the weekly group (n=2) and changed the iron preparation. In two women iron supplementation was discontinued because of severe vomiting. Both the patients had Hb <12 gm/dL at the start of their pregnancies and received only a dietary source of iron. Repeat haemoglobin levels at 34 weeks period of gestation were > 11gm/dL (n1 = 11.2 gm/dL; n2=11.3 gm/dL).

At baseline, 41.8% of the women in the daily group (n=23) and 25.5% of the women in the weekly group (n=14) had hemoglobin concentration

<11gm/g L. of the women who were in the first trimester of pregnancy, (n=74, Daily = 33, Weekly = 41), 42.42% of the daily (n=14) and 14.63% of the weekly (n=6) group were anemic, with a hemoglobin concentration<11gm/d L. of the women in the second trimester (n=36, Daily = 22, Weekly = 14), 45.45% of the daily (n=10) and 57.14 % of the weekly (n=8) group had hemoglobin < 11gm/dL.

At baseline 69% (38 out of 55) and 49.1 % (27 out of 55) of women supplemented daily had serum ferritin values <20ng/ml and <12 ng/ml, respectively. For the women supplemented weekly this prevalence was 87.2% (48 out of 55) and 69% (38 out of 55) respectively.

Both Hb concentration < 11gm/dL and serum ferritin concentration <12ng/ml were found in 23.6% (13 out of 55) of the group supplemented daily and in 20% (11 out of 55) of the group supplemented weekly. So overall prevalence of IDA in this population was 21.81% (24 out of 110) whereas 60.9% (67 out of 110) were iron deficient and 39.09% (43 out of 110) of the population were iron deficient but non-anemic.

At the end of the study, the prevalence of anemia had increased in the weekly group 25.5% to 41.8% (14 out of 55). In the daily group the prevalence had decreased from 41.8% to 25.5% (14 out of 55).

The prevalence of iron deficiency as measured by serum ferritin concentrations <12ng/ml was 49.1% (27 out of 55) and 80% (44 out of 55) in women supplemented daily and weekly respectively at the end of the study.

Prevalence of IDA in the daily supplemented group had decreased from 23.6% to 12.7% whereas in the weekly group it had increased from 20% to 34.5% (Table 2).

Table 2: Prevalence of iron deficiency and anemia in the supplementation groups before and after treatment.

	Before Treatment (n=55)	After Treatment (n=55)
Daily Group (n=55)		
Hb con. <11gm/dl	41.8% (n=23)	25.5% (n=14)
Se Ferritin <12ng/ml	49.1% (n=27)	49.1% (n=27)
Both Hb <11gm/dl and Se Fe < 12ng/ml	23.6% (n=13)	12.7% (n=7)
Weekly group (n+55)		
Hb con. <11gm/dl	25.5% (n=14)	41.8%(n=23)
Se Ferritin < 12 gm/ml	69.0% (n=38)	80.0%(n=44)
Both Hb,11gm; dl and Se Fe < 12ng/ml	20% (n=11)	34.5%(n=19)

In the beginning, the mean hemoglobin level in the daily supplemented group was 11.32± 1.04 gm/dL and in the weekly supplemented group 11.63±0.91 gm/dL (p=0.164), Initial mean serum ferritin level in the daily group was 18.41±21.97ng/ml and was higher than in the weekly group (9.96±8.74ng/ml). The difference was statistically significant (p=0.027).

In the daily group there was 0.37±1.48 gm/dL increase in hemoglobin (p=0.116) at the end of supplementation; the comparative change in the weekly group was – 0.21±1.45gm/dL (p=0.316). Thus there was no significant increase in hemoglobin in either group.

Mean serum ferritin level increased marginally in the daily group from 18.41±21.97 ng/ml to 21.24±26.25 ng/ml (mean rise 2.83±24.98ng/ml, 9p=0.477) but the rise was not statistically significant. In the weekly group the mean serum ferritin level decreased from 9.96±8.74ng/ml to 9.21±12.15ng/ml (mean fall – 0.75±11.41ng/ml, p=0.68) but the failure was not statistically significant.

The final ferritin level in the weekly group was significantly lower (p=0.01) than the corresponding values in the daily group. However the initial values were also significantly lower. The change in the ferritin level in the daily group was not significantly different from that in the weekly group (p=0412).

Among the RBC indices, - hematocrit, MCV, and MCH levels were not different between the two treatment groups either at the start or at the end of supplementation. In the weekly supplemented group, there was a marginal fall in the values of HCT, MCV, and MCH after an average of 17 weeks of iron supplementation, but these within-group changes were not statistically significant.

On the other hand, in the daily supplemented group – there was a minimal increase in mean HCT, MCV, and MCH values, though not statistically significant. Initial and final MCHC levels were significantly higher in the daily group (p<0.05) as compared to the weekly group.

However, the mean increase in MCHC seen either group was not significantly different (0.51±2.34 vs. 0.41±2.09gm. dl, p=0.221) between the groups (Table 3).

Table 3: Haematological values at the beginning and end of the supplementation period.

Study group	Beginning	End	Difference	p-value
Daily group(n=55) • Hb (mg/dL)	11.32±1.04	11.70±1.13	0.37±1.48	0.116
• HCT (%)	34.06±2.49	34.38±3.06	0.31±3.34	0.558
• MCV (fl)	86.31±4.51	87.35±7.04	1.04±5.38	0.226
• MCHC (pg)	29.15±1.79	29.70±2.69	0.55±2.41	0.154
• MCHC (gm/dL)	33.43±2.14	33.94±1.98	0.51±2.34	0.173
• Se.ferritin(ng/ml)	18.41±21.97	21.24±26.25	2.83±24.98	0.477
Weekly group(n=55)				
• Hb (mg/dL)	11.63±0.91	11.42±1.35	-0.21±1.45	0.361
• HCT (%)	34.94±2.87	34.73±3.68	-0.21±3.31	0.691
• MCV (fl)	87.63±521	86.36±7.56	-1.26±6.33	0.213
• MCHC (pg)	29.00±2.06	28.43±2.80	-0.57±2.54	0.163
• MCHC (gm/dL)	32.51±1.79	32.92±1.67	-0.41±2.09	0.221
• Se. ferritin (ng/ml)	996±8.74	9.21±12.15	-0.75±11.41	0.680

Table 4: Haematological values at baseline and follow up.

Hemoglobin	Week	Daily		Weekly		Difference gm/dL	P-value
		n	gm/dl	N	gm/dl		
Baseline	0	55	11.32±1.04	55	11.63±0.91	0.31	0.164
1st Visit	4	37	11.34±0.74	46	14.11±16.52	2.77	0.387
2nd Visit	12	51	11.38±0.88	51	11.21±0.96	-0.17	0.416
Final visit	18	55	11.70±1.13	55	11.42±1.3	-0.28	0.314

Se. ferritin	Week	Daily		Weekly		Difference ng/ml	P-Value
		N	ng/ml	N	ng/ml		
Baseline	0	55	18.41±21.97	55	9.96±8.74	-8.45	0.027*
Final visit	18	55	21.24±26.25	55	9.21±12.15	-12.03	0.10*

MCV	Week	Daily		Weekly		Difference FI	P-Value
		N	FI	N	FI		
Baseline	0	55	86.31±4.51	55	87.63±5.21	1.32	0.228
1st visit	4	28	85.12±7.85	28	85.62±5.78	0.41	0.871
2nd Visit	12	35	86.88±6.93	45	84.19±5.21	-2.69	0.203
Final visit	18	55	87.35±7.04	55	86.36±7.56	-0.99	0.546

The changes in hemoglobin and serum ferritin were related to the initial concentration of these variables (Table 4).

For those women who had a hemoglobin concentration <11gm/dL at the beginning, the rise in hemoglobin concentration was significantly greater at the end in the daily supplemented group as compared to the weekly group (1.44±1.51 gm/dl vs. 0.12±1.05 gm/dl, p=0.015).

The mean serum ferritin level in the daily supplemented anemic subgroup increased from 16.23±21.42 ng/ml to 21.14±26.66 ng/ml. On the other hand, the mean serum ferritin level showed a decreasing trend from 9.00±7.33ng/ml to 7.50±5.45ng/1 in the weekly anemic subgroup.

However, when the changes in the serum ferritin level which occurred in each group were compared, there was no significant difference (p=0.415) between the two intervention groups.

For those women who started pregnancy with hemoglobin concentration >11gm/dL, no statistically significant difference was noted between the two intervention groups with respect to change in hemoglobin (p=0.871) and serum ferritin concentration (p=0.741) at the end of the study period.

Discussion

Anemia is the most common nutritional deficiency disorder in pregnancy, worldwide. In India, approximately 62–88% of pregnant women are anemic [12]. Supplementation programs have been implemented since 1971 in India, and the dose of supplementation has been increased up to 100 mg of elemental iron per day, yet the magnitude of the problem remains unchanged [12]. It is recognized that one of the major problems of daily supplementation schedule is lack of compliance because of the high incidence of gastrointestinal side effects.

Added to this are the recent concerns of molecular damage as a result of iron over-dosage [2]. Weekly iron supplements have been tried in some populations, with equal or sub-optimal benefits compared with those of daily supplementation [8,10,13].

Since the effectiveness of large-scale supplementation programs has never been established, the International Nutritional Anaemia Consultative Group, the WHO and UNICEF are considering the option of intermittent iron supplementation as a therapeutic protocol [14].

Beaton and McCabe, in a meta-analysis of 21 published and unpublished studies regarding daily versus intermittent iron supplementation in various populations, found that there was a higher final hemoglobin concentration associated with the daily administration of iron [15]. From India, Gomber et al. studied daily versus weekly iron supplements in 80 pregnant women and concluded that weekly supplementation was as effective as daily [16].

Table 5: Prevalence of iron deficiency and anemia.

	Category	Rajaratnam J et al [18]	Present study
I.	No iron deficiency, no anemia	25.2%	27.3%
II.	Storage iron depletion, not anaemic	7.1%	39.0%
III.	Iron deficiency anemia	29.5%	21.8%
IV.	Anemia, but not iron deficient	38.3%	11.8%

However, only 56 women could be followed up until the time of final analysis and the women were predominantly non-anemic at the time of recruitment. The present study was therefore planned to address the feasibility of giving weekly

Supplements to pregnant Indian women. The study population consisted of a blend of urban and rural pregnant women attending the antenatal clinic of a referral center. A placebo group was not included because of ethical reasons. Because women with hemoglobin <10g/dL were excluded from the study, it was not possible to calculate the exact prevalence of anemia. At the baseline, the overall prevalence of iron deficiency was 60.9% (67 out of 110) and the prevalence of IDA was 21.81% (24 out of 110). 11.81% of cases were anemic but not iron deficient. A study under a similar setting reported the prevalence of anemia in pregnancy was 30% in the urban area of Delhi [17]. Mean serum ferritin concentration in 110 women was 14.18±17.15 ng/ml, this mean level is lower than those reported by other studies [19]. In the present study, weekly supplementation was as effective as daily supplementation in maintaining the hemoglobin level in pregnancy. However, because the majority of the pregnant women were non-anemic to start with, there was no further significant increase in the hemoglobin level in either group. In contrast, studies conducted in Indonesia, Malawi, and China have dealt with rural pregnant women who were primarily anemic. Hence a rise in the hemoglobin level was evident after iron therapy and a significant rise in hemoglobin level occurred in both treatment groups. At enrollment, the log serum ferritin level in the daily supplemented group was higher than that in the weekly supplemented group (P = 0.08). The difference in these values despite successful randomization can probably be explained by the fact that the sample size was small: five patients in the daily group had serum ferritin levels ≥90 ng/mL, which resulted in an increase in the mean value. The final ferritin level was lower in the weekly Group after adjusting for the initial difference and for other covariates. Although the final hemoglobin levels were not different between the two groups, daily supplementation proved to be superior to weekly supplementation in the anemic subgroup. Among the non-anemic women, more women in the weekly group (10/30, 33.3%) became anemic at the 34-week period of gestation compared with those in the daily group (5/23, 22%). Hemoglobin concentration increased to >11 g/dL by 34 weeks' gestation in anemic women receiving daily supplementation, but anemic women receiving weekly supplementation continued to be anemic after an average 17 weeks of iron supplementation. However, the majority of women who had become anemic at 34 weeks had hemoglobin concentrations between 10.5 and 10.9 g/dL, which according to the Center for Disease Control criteria [20] is approximately the fifth percentile of hemoglobin level at that period of gestation. This could be thus explained by physiological hemodilution. In a study by Milman et al., based on the hemoglobin concentrations seen in 206 pregnant women, it was concluded that a cut-off value of 10.5 g/dL instead of 11 g/dL should define pregnancy anemia in the second and third trimesters [21]. Low compliance with iron supplementation programs has been widely reported, with 60% of women verbally reporting compliance and only 32–36% of women complying with the prescribed schedule when checked using stool tests [22-24].

Table 6: Haemoglobin levels in various studies.

Study	Daily supplementation		Intermittent Supplementation	
	Initial Hb gm/dl	Final Hb gm/dl	Initial Hb gm/dl	Final Hb gm/dl
Ridwan et al [6]	10.1±0.6	10.9±0.7	9.8±0.8	10.6±0.7
Young et al [8]	10.5±1.4	11.3±1.8	10.4±1.5	10.5±1.4
Mumtaz et al [25]	9.2±1.4	11.3±1.8	9.5±1.0	10.0±1.2
Present study	11.3±1.0	11.7±1.1	11.6±0.9	11.4±1.3

Table 7: Serum ferritin levels in the two intervention groups.

Study	Daily suppl.		intermittent suppl.	
	Initial ferritin ng/ml	Final ferritin ng/ml	Initial ferritin ng/ml	Final ferritin ng/ml
Ridwan et al [6]	28.0±19.2	27.7±19.8	23.2±20.5	20.5±16.9
Mumtaz et al [25]	23.8±29.7	41.6±34.9	23.0±33.7	27.6±31.5
Present study	18.41±21.97	21.24±26.25	9.96±8.74	9.21±12.15

Table-8: Haemoglobin response in the anemic subgroup (Hb<11gm/dl).

Study	Daily supplemented			Intermittent Supplemented		
	Initial Hb gm/dl	Final Hb gm/dl	▲gm/dl	Initial Hb gm/dl	Final Hb gm/dl	▲gm/dl
Mumtaz et al [25]	9.26±1.41(n=100)	11.36±1.83 (n=55)	2.10	9.58±1.06(n=91)	10.09±1.23 (n=50)	0.51
Ridwan et al [6]	10.1±0.6(n=45)	10.9±0.7(n=45)	0.8±0.8	9.8±0.8(n=54)	10.6±0.7(n=54)	0.8±0.7
Young et al [8]	(n=70)		0.63±1.26	(n=66)		0.59±1.18
Present study	10.30±0.31 (n=23)	11.74±1.34	1.44±1.51	10.48±0.26 (n=14)	10.60±0.97	0.12±1.05

Table-9: Haematological indices in pregnancy.

Analysis	Therapy	<15 weeks		26-30 weeks		33-34 weeks	
		Taylor et al	Present	Taylor et al	Present	Taylor et al	Present
Hb gm/dl	Daily iron	12.42	11.32	11.42	11.38	11.80	11.70
	No iron	12.23		11.22		11.04	
	Weekly iron		11.63		11.21		34.42
HCT %	Daily iron	35.98	34.06	33.27	29.04	34.42	34.38
	No iron	35.25		32.74		32.41	
	Weekly iron		34.94		33.70		34.73
MCV fl	Daily iron	83.62	86.31	87.63	86.88	87.79/td>	87.35
	No iron	84.63		88.03		86.01	
	Weekly iron		87.63		84.19		86.36
MCH pg	Daily iron	28.87	29.15	30.20	29.45	29.22	29.70
	No iron	29.35		30.32		29.43	
	Weekly iron		29.00		29.17		28.43
MCHC gm/dl	Daily iron	34.27	33.43	34.12	35.33	34.13	3394
	No iron	34.49		34.19		33.92	
	Weekly iron		32.51		32.64		32.92

Table-10: Comparison of compliance between the daily and weekly supplemented group.

Studies	Compliance checked	Daily	Weekly	P-value
Ridwan et al [6]	Stool test	54.3%	62.2%	NS
Young et al [8]	Self-reporting and pill counting	59.8%	76.0%	0.011*
	Stool test	61.8%	59.6%	NS
Present study	Self-reporting and pill counting/td>	40%	85.5%	<0.001*

Table-11: Relation between side effects and compliance.

Studies	Side effects (SE)			Compliance	
	Daily	Weekly	P-value	SE+ve	SE-ve
Young et al [8]	17%	6%	0.01*	60%	68%
Ridwan et al [6]	16.2%	18.3%	NS	20.8%	63.5%
Present study	49%	10.9%	<0.01*	16.6%	66%

*Significant

Table-12: Relation between maternal hemoglobin, birth weight, and period of gestation.

Studies	Maternal Hb/serum ferritin	Birth of wt. (gm) (Mean±SD)	POG at delivery (weeks) (Mean±SD)
Agarwal et al [26]	Hb 8.6-10.9 gm/dL (n=17)	2760.2±410.50	39.4±1.64
	Hb>11gm/dL (n=21)	2759.5±352.35	37.7±5.49
Bhargava et al [27]	Se Fe>10 ng/ml (n=45)	2518.75±508.00	37.55±2.05
	Se Fe>10 ng/ml (n=263)	2552.33±566.06	37.59±1.98
Present study	Hb <11 gm/dl (n=37)	<2.5kg (13.5%)	38.66±1.17
	Hb>11 gm/dl (n=73)	<2.5kg (9.5%)	38.33±1.42

In the present study, 67.7% of women in the daily group were non-compliant and gastrointestinal side-effects were responsible for this in 75% of cases. In the weekly group, only 15% did not comply with the prescribed schedule, the major reason being forgetting to take iron pills after an interval of a week. In the present study, though the anemic subgroup supplemented weekly did not show any rise in the final hemoglobin concentration, the effect was not translated into adverse pregnancy outcomes like low birth weight or preterm deliveries. The results are in accordance with earlier studies, in which mild anemia in pregnancy was not related to an increased incidence of preterm or low birth weight babies, although babies born to severely anemic mothers did have lower birth weights and shorter gestation [17].

Conclusion

To conclude, overall, the intermittent iron supplementation did not differ from the daily supplementation in terms of hematological response. Also the subjects had low-grade anemia initially and actually a very small dosage of iron was

Needed for them to reach their optimal hemoglobin concentrations. These may be the reasons that no significant difference was observed between the two treatment regimens. The same holds true for the present study where all women had hemoglobin level ≥ 10gm/dl and were supplemented for 17 weeks on an average. The issue of whether weekly iron supplementation leads to folic acid deficiency as well because the daily recommended allowance of 400µg/day is not fulfilled in a weekly schedule was not investigated.

There was no evidence of macrocytosis in women who remained anemic at the end of supplementation. Serum folic acid levels were not measured. Iron supplementation works in a complex multidimensional context that includes socio-cultural, economic, and political facets. It is important to look at the effectiveness of otherwise efficacious regimens in field conditions and not take decisions based on perceived efficiencies alone. Further studies, especially in developing countries, on a large scale are required to consolidate the basis of implementing weekly iron supplementation programs.

What does the study add to the existing knowledge?

In non – anemic pregnant women, there is no demonstrable benefit of daily supplementation in terms of hemoglobin rise, improved ferritin levels, or perinatal outcome. On the other hand, there are significantly fewer side effects and patients are happier and more compliant with the weekly regimen. Intermittent iron dosing as a prophylactic supplementation can adequately meet the increased demands of pregnancy even if they are iron deficient.

However in anemic women, even with mild anemia, daily supplementation appears to be superior to weekly supplementation and the present study shows less than optimal benefits in terms of raising hemoglobin in the weekly supplemented group, though small sample size precludes statistical relevance.

Meanwhile it appears that though an effective alternative for prophylactic supplementation, for therapeutic supplementation in mild and moderately anemic women, larger field base trials are required to substantiate the efficacy of intermittent iron supplementation as a public health strategy especially in a developing country like India.

Author's contribution

Dr. Shrikrishna Kumar Agrawal: Study design, concept

Dr. Monika Jindal: Statistical analysis, manuscript preparation

Reference

01. Vijayaraghavan K, Brahmam GN, Nair KM, Akbar D, Rao NP. Evaluation of national nutritional anemia prophylaxis programme. Indian J Pediatr. 1990;57(2)183-190. doi: [Article:https://doi.org/10.1007/bf02722084] [Crossref]

02. Solomons NW, Pineda O, Viteri FE, Sandstead HH. Studies on the bioavailability of zinc in humans- mechanism of the intestinal interaction of non-heme Fe and Zinc. J Nutr. 1983;113(2)927-935. doi: [Article:https://doi.org/10.1093/jn/113.2.337] [Crossref]

03. O'?Neil-Cutting MA, Crosby WH. Blocking of iron absorption by a preliminary oral dose of iron. Arch Intern Med. 1987;147(3)489-491. [Crossref]

04. Viteri FE. Weekly compared with daily iron supplementation. Am J Clin Nutr. 1996;63(4)610-611. doi: [Article:https://doi.org/10.1093/ajcn/63.4.610] [Crossref]

05. Viteri FE. A new concept in the control of iron deficiency- community based preventive supplementation of at risk groups by the weekly intermittent iron supplements. Biomed Environ Sci. 1998;11(1)46-60. [Crossref]

06. Ridwan E, Schultink W, Dillon D, Gross R. Effects of Weekly iron supplementation on pregnant Indonesian women are similar to those of daily supplementation. Am J Clin Nutr. 1996;63(6)884-890. doi:[Article:https://doi.org/10.1093/ajcn/63.6.884] [Crossref]

07. Liu XN, Zhang JL, Yen HL, Viteri FE. Haemoglobin and serum ferritin levels in pregnant Chinese women in response to weekly iron supplements. [Abstract] In;7th Asian Congress of Nutrition. Beijing, 1995. [Crossref]

08. Young MW, Lupafya E, Kapendra E, Bobrow E. The effectiveness of weekly iron supplementation in pregnant women of rural northern Malawi. Tropical Doctor. 2000;30(2)84-88.
doi:
[Article:https://doi.org/10.1177/004947550003000210][Crossref]

09. Rajaratnam J, Abel R, Ganesan C, Jayaseelan SA. Maternal anaemia- A persistent problem in rural Tamil Nadu. Natl Med J Ind. 2000;13(5)242-245.
[Crossref]

10. World Health Organization. The prevalence of anaemia in women- a tabulation of available information. 2nd ed; WHO. Geneva 1992 (WHO/MCH/MSM 92.2).
Available at[Article:https://apps.who.int/iris/handle/10665/58994][Crossref]

11. Svanberg B. Iron absorption in early pregnancy – a study of the absorption of non-haem iron and ferrous iron in early pregnancy. Actabstet Gynecol Scand. 1975;48;69-85.
doi: [Article:https://doi.org/10.3109/00016347509156331][Crossref]

12. Taylor DJ, Ling T. Haematological changes during normal pregnancy- Iron induced macrocytes: Br J Obstet Gynaecol 1976;83(10)760-767.
doi: https://doi.org/10.1111/j.1471-0528.1976.tb00740.x [Crossref]

13. Taylor DJ, Lind T. Red cell mass during and after normal pregnancy. Br J Obstet Gynaecol. 1979;86(5)364-370.
doi: [Article:https://doi.org/10.1111/j.1471-0528.1979.tb10611.x][Crossref]

14. Stoltzfus RJ, Dreyfuss ML. Guidelines for the use of iron supplements to prevent and treat iron deficiency anemia. Washington, DC; Ilsi Press. 1998.
Available at:[Article][Crossref]

15. Beaton GH, McCabe GP. Micronutrient Initiative- Efficacy of intermittent iron supplementation in the control of iron deficiency anaemia in developing countries- an analysis of experience; final report to the Micronutrient Initiative. Micronutrient Initiative, Ottawa, ON. CA; 1999.
Available at [Article][Crossref]

16. Agarwal KN, Gomber S, Bisht H, Som M. Anemia prophylaxis in adolescent school girls by weekly or daily iron-folate supplementation. Indian Pediatr. 2003;40(4)296-302.
[Crossref]

17. Mukhopadhyay A, Bhatla N, Kriplani A, Pandey RM, Saxena R. Daily versus intermittent iron supplementation in pregnant women-hematological and pregnancy outcome. J Obstet Gynaecol Res. 2004;30(6)409-417.
doi:[Article:https://doi.org/10.1111/j.1447-0756.2004.00223.x][Crossref]

18. Rajaratnam J, Abel R, Ganesan C, Jayaseelan SA. Maternal anaemia- a persistent problem in rural Tamil Nadu. Nat Med J India. 2000 ;13(5)242-245.
[Crossref]

19. Beard JL. Weekly iron intervention- the case for intermittent iron supplementation. Am J Clin Nutr. 1998;68(2)-209-121.
doi: [Article:https://doi.org/10.1093/ajcn/68.2.209] [Crossref]

20. Younes M, Eberhrdt I, Lemoine R. Effect of iron overload on spontaneous and xenobiotic induced lipid peroxidation in vivo. J Appl Toxicol. 1989;9(2)103-108.
doi:
[Article:https://doi.org/10.1002/jat.2550090206] [Crossref]

21. Knutson MD, Walter PB, Ames BN, Viteri FE. Both iron deficiency and daily iron supplements lipid peroxidation in rats. J Nutr. 2000;130(3)621-628.
doi: [Article:https://doi.org/10.1093/jn/130.3.621][Crossref]

22. Viteri FE, Xunian L, Tolomei K, Martin A. True absorption and retention of supplementation iron is more efficient when iron is administered every three days rather than daily to iron-normal and iron deficient rats. J Nutr. 1995;125(1)82-91.
doi: [Article:https://doi.org/10.1093/jn/125.1.82] [Crossref]

23. Schultink W, Gross R, Gliwitzki M, Karyadi D, Matulessi P. effect of daily vs twice weekly iron supplementation in Indonesian preschool children with low iron status. Am J Clin Nutr. 1995;61(1)111-115.
doi: [Article:https://doi.org/10.1093/ajcn/61.1.111] [Crossref]

24. Beard JL. Effectiveness and strategies of iron supplementation during pregnancy. Am J Clin Nutr. 2000;71(5)1288S-1294S.
doi:
[Article:https://doi.org/10.1093/ajcn/71.5.1288s]
[Crossref]

25. Mumtaz Z, Shahab S, Butt N, Ral MA, DeMuynck A. Daily iron supplementation is more effective than twice weekly iron supplementation in pregnant women in Pakistan in a randomized double-blind clinical trial. J Nutr. 2000;130(11)2697-2702.
doi: [Article:https://doi.org/10.1093/jn/130.11.2697]
[Crossref]

26. Agarwal A, Rai S, Prasad R. Impact of the Integrated Child Development Services (ICDS) on Maternal Nutrition and Birth Weight in Rural Varanasi KN Agarwal, DK Agarwal. Indian Pediatr. 2000;37(12)1321-1327.
[Crossref]

27. Bhargava M, Iyer PU, Kumar R. Relationship of maternal serum ferritin with foetal serum ferritin, birth weight and gestation. J Trop Pediatr. 1991;37(4)149-152.
doi:
[Article:https://doi.org/10.1093/tropej/37.4.149]
[Crossref]