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Efficacy of intermittent iron versus daily iron in antenatal women

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Abstract
Aim: This study was done to determine if alternate day oral iron as effective as daily oral iron in antenatal women including those with mild anemia.
Methods & Material: A prospective randomised trial was done in 215 antenatal women attending a tertiary centre in South India. Group 1 received 100mg of elemental iron daily and group 2 received 100mgs of elemental iron on alternate days. Haemoglobin was estimated in all the trimesters and change in Haemoglobin from baseline and at 32-34 weeks were estimated. Side effects and neonatal outcomes were analysed. Further analysis were done within groups depending upon the Haemoglobin levels.
Results: There was no difference in Haemoglobin levels between the two groups. The response was better in patients with mild anemia in both groups, however when iron was given daily in mildly anemia women the increase in Haemoglobin was better than alternate iron therapy.
Conclusion: Intermittent iron is as effective as daily iron.

Keywords: Haemoglobin, daily iron, intermittent iron, iron therapy in pregnancy, anemia in pregnancy

Introduction

Anaemia complicating pregnancy is one of the most common medical disorders of pregnancy. The WHO [1] has defined anaemia as a Haemoglobin less than 11gms/dl in the first and third trimester and a Haemoglobin of less than 10.5gms/dl in the second trimester. Any Haemoglobin less than the 5th percentile for a given gestation is defined as anaemia by CDC [2]. Globally about 58.25 million women are found to be anaemic during pregnancy and 95% of them belong to the developing world [3]. In India as per the population based survey in 2016 it was found that about 50% of pregnant women were anaemic [4]. Anaemia is a direct and an indirect cause of maternal mortality and causes around 13% of all maternal deaths and about 20% in South East Asia [5].

As part of a global strategy to prevent anaemia, WHO has recommended that all pregnant women be given 60mgs of elemental iron with 400mgs of folic acid every day prophylactically[6]. However in the event of iron deficiency anaemia, higher doses are prescribed. Oral iron is associated with many undesirable side effects causing poor compliance. An ideal dosing schedule is yet to be found, which patients will not default and yet give the desired results.

There has been lot of research in iron metabolism over the past two decades.

First is the presence of protein Hepcidin which regulates iron absorption [7], second is the mucosal turn over time which is said to occur once in 3 to 5 days. Thus after a given dose, further supplementation with iron until turn overtime is completed might lead to impaired absorption since the cells are already saturated [8]. Excess iron may cause oxidative stress and other side effects [9]. This has changed the thinking that intermittent iron might work as well. Subsequent to this there are many studies which state that iron two or three times per week or even once a week might be all that is required. Most of these studies have been done in pregnant women who had normal haemoglobin levels.

The WHO in a recent guideline has suggested administration of weekly iron of 120mgs with 2.8mgs of folic acid in pregnant women in areas where the prevalence of anaemia is less than 20% [10].

In India, the practise is still to administer daily iron during pregnancy. Being an area where the prevalence of anaemia is high, it would be worthwhile to know the efficiency and advantages of intermittent iron and hence this study was conducted to determine the usefulness of intermittent iron in both mildly anaemic and non anaemic pregnant women.

Materials and Methods

This was a prospective observational study conducted at a teaching hospital in South India. 215 pregnant women attending the antenatal OPD were randomly recruited for this study. 105 pregnant women from Unit 1 were assigned to daily iron and formed group 1 and 110 pregnant women from Unit 2 were given alternate day iron and were assigned as group 2. During the first visit between 10 to 14 weeks investigations like CBC, Peripheral smear and serum ferritin were done. This helped to rule out thalassemia which is not very uncommon in this area. Ferrous tablets containing 100mgs of elemental iron and 500mgs of folic acid was used after completion of 13 weeks and continued till delivery.

Exclusion criteria: Were Haemoglobin less than 9gms in the first trimester, history of haemtological disorders like sickle cell or thalassemia and history of autoimmune disorders.

Inclusion criteria: All patients attending OPD from at least 12 weeks of pregnancy. The patients were asked to take iron at night before food or at least one hour after food. They were asked to report if they had any side effects like vomiting, diarrhoea, heart burn or constipation. Repeat Haemoglobin was done in the second trimester and around 32 to 34 weeks to assess the Haemoglobin status of the individual. If the Haemoglobin fell to less than 8gms they were advised parenteral iron. Haemoglobin was done using Coulter LH 780 Haematology Analyser method. The maternal and fetal outcomes were noted.
Patients who did not have their delivery in our institution and if the Haemoglobin levels were not done in the third trimester, were excluded from the final analysis and two patients who were given parenteral iron were also excluded from final analysis.

Statistical Analysis

The categorical variables were analysed using chi square test and the continuous variables were analysed using test and ANOVA. P value of .005 was taken as significant. Both groups were compared in regard to mean change from baseline Haemoglobin to Haemoglobin at the 2nd and 3rdtrimester.
The groups were further subdivided into three groups based on Haemoglobin levels. Group A had Haemoglobin level between 9 to 11gms, Group B had Haemoglobin levels between 11.1 to 13gms and Group C had Haemoglobin levels more than 13gms and analysis done within the subgroup with regards to the change in Haemoglobin levels in the first and last trimester.

Results

Total of 215 pregnant women were included in this study 105 in the daily group and 110 in the alternate group. A total of 173 women, 80 in group 1 (daily Iron) and 93 in group 2 (alternate day Iron) were analysed and the attrition was mainly due to change of place for delivery, or incomplete data and investigations. Table 1 shows the age distribution in both groups and Table 2 shows the parity.

Table 1: Age

Age Yrs	Daily Regimen	Alternate Iron
<20	1	3
	1.3%	3.2%
21-25	34	31
	42.5%	33.3%
26-30	36	48
	45.0%	51.6%
>30	9	11
	11.3%	11.8%
Total	80	93

Table 2: Parity

	Daily Regimen	Alternate Iron
Primi	53	62
	66.25%	66.66%
Multi	27	31
	33.75%	33.33%
Total	80	93

The distribution of age and parity were similar in both groups. Table 3 shows the mean Haemoglobin levels in all trimesters in both groups which showed that the mean Haemoglobin levels were almost identical in both groups. The levels were higher in the first trimester and third trimester and slightly lower in the second trimester as expected due to haemodilution.

Table 3: Mean Hemoglobin in all trimester

Trimester		Daily regimen (N=80)	Alternate regimen (N=93)
1st trimester	Mean Hb	11.553	11.983
	SD	(1.2447)	(1.1462)
2nd trimester	Mean Hb	11.138	11.271
	SD	(0.9611)	(0.8489)
3rd trimester	Mean Hb	11.3065	11.382
	SD	1.1487	1.1218

The relationship between the Haemoglobin level and the ferritin level is shown in Fig1.

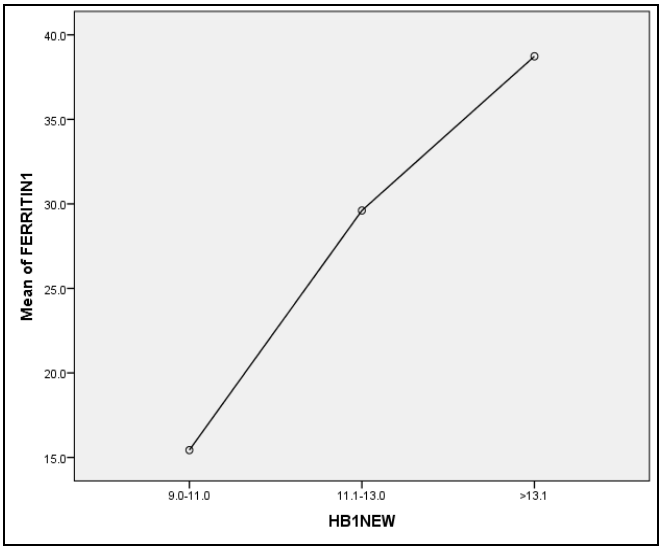

Fig 1: Relationship between the Haemoglobin level and the Ferritin level

38 women had ferritin levels less than 12ngm/dl. 24 in the daily group and 14 in the alternate group had ferritin less than 12 ngm/dl.
Table 4 shows the side effects of oral iron in both groups. Side effects were much lesser in the alternate iron group and so also was the compliance, which was found to be significant statistically with a P value of <001.

Table 4: Side effects

Side effects	Daily regimen (N=80)	Alternate regimen (N=93)
Vomiting	38	5
Constipation	30	8
Diarrhoea	2	1
Metallic taste	5	2
Bloatedness	10	2

Both groups were analysed as subgroups with the Haemoglobin levels in each trimester as shown in Table 5. This table shows that the response and Haemoglobin rise was better in women with mild anemia in both groups and the rise in Haemoglobin was better in the daily group.

Table 5: Analysis of haemoglobin in different sub groups in all trimesters

Hb gm/dl		1st trimester	2nd trimester	3rd trimester
9.0-11.0	Daily regimen N=26	10.085	10.872	11.1960
	Alternate regimen N=22 cases	10.395	10.629	10.9719
11.1-13.0	Daily regimen N=45 cases	11.996	11.107	11.2500
	Alternate regimen N=55 cases	12.169	11.375	11.3611
>13.1	Daily regimen N=9 cases	13.578	12.033	11.9625
	Alternate regimen N=16 cases	13.525	11.756	12.0333
Total	Daily regimen N=80 cases	11.553	11.138	11.3065
	Alternate regimen N=93 cases	11.983	11.271	11.3823

There were no preterm deliveries and the birth weight of babies was similar as shown in Table 6.

Table 6: Birth weight

	Hb	Number	Mean birth weight
Daily regimen (N=80)	9.0 – 11.0	25	3.0548
	11.1 - 13.0	45	2.9983
	>13.1	9	3.2938
	Total	80	3.0487
Alternate regimen (N=93)	9.0 – 11.0	22	3.0514
	11.1 - 13.0	55	2.9898
	>13.1	16	2.9106
	Total	93	2.9908

Discussion

In our study 80 women with a mean Haemoglobin 11.5gms/dl were given daily iron and 93 women with a mean Haemoglobin of 11.93gms/dl were given alternate iron. The third trimester Haemoglobin was 11.30gms/dl in the daily group and 11.38gms/dl in the alternate group showing that in both the treatment groups the Haemoglobin was almost the same.

WHO recommends 30-60mgs of elemental iron for all pregnant women depending on the prevalence of anaemia. This lower dose of 30mgs by WHO supersedes the previous recommendation of 60mgs taking into account the side effects and iron pharmokinetics [11].

The National iron plus initiative of India recommends iron folic acid [IFA] supplementation of 100 mg elemental iron and 500 mgs of folic acid every day for at least 100 days starting after the first trimester at 14–16 weeks of gestation for all non-anemic pregnant women followed by the same dose for 100 days postpartum [12].

Currently intermittent iron supplementation has been accepted for prophylaxis except in antenatal programmes for which debate is still ongoing.

In the past few years many studies have proven the hypothesis that intermittent iron is as effective as daily iron in terms of Haemoglobin change with the added advantage of having less side effects and being cost-effective. In spite of this information the change to intermittent therapy has not yet been implemented, maybe, since the prevalence is so high and further studies are warranted.

Cochrane in 2015 reviewed 21 trials of daily iron versus intermittent iron and stated that while there was no difference between groups for any maternal or fetal outcomes, the intermittent groups had less side effects [13].

Pena-rosa [14] suggested that women receiving intermittent iron had similar maternal and fetal outcomes. Study by Mukhopadhyay [15], Goonewardene [16] and ZInatossadaat [17] in have all suggested that intermittent iron is as effective as daily dosing.

Our study also proved that intermittent iron was as good as daily iron.

The second observation was that in patients who were found to have Haemoglobin between 9 to 11gms/dl, the rise in Haemoglobin was better in these patients with mild anaemia than non-anaemia and a mean increase of 1.1gm/dl was noted in daily group and 0.60gms/dl in the alternate group. The patients in the group with Haemoglobin between 11.1 to 13gms/dl and more than 13gms/dl did not show an increase, but showed a slight fall in Haemoglobin level from baseline.

There were two observations different in our study when compared to many studies. The first observation was that post treatment Haemoglobin did not show an increase from baseline as many studies have shown. However Adaji [18] in his Nigerian study between once and twice daily dosing has shown a fall in baseline Haemoglobin from 11.1gms/dl and 11gms/dl to 10.2gms/dl and 10.5gms/dl respectively in both arms. Similar fall in Haemoglobin has been noted by Okwara [19] who showed a fall from 11.2gms/dl in the first trimester to 10.4 gms/dl in the third trimester. In our study too, in the daily group the fall in Haemoglobin level was 0.2gms/dl and was 0 .6gms/dl in the alternate day group which was not statistically significant.

The second observation was that Haemoglobin improvement was better in women with anaemia in both groups. Although the final Haemoglobin was not very different in both groups, daily iron proved to be slightly better than alternate iron. The maximum oral dose per day is only 160mgs/day. Hence doubling the dose to twice daily is not beneficial, anaemic women would do well by just once daily dosing

Intake of iron is generally associated with untoward side effects like vomiting, constipation, dark stools, diarrhoea and a metallic taste in the tongue. A few rare myths discovered during the study was the belief that babies might be darker or be heavier which lead to women refraining from taking the medications. Side effects were less when given on alternate days, making women more compliant. According to a study by Khalafalloh [20] the side effects of oral iron include gastro intestinal disturbances characterised by colicky pain, vomiting, diarrhoea and constipation which occurred in about 50% of patients. Many patients taking more than 30mgs of iron per day have side effects causing them to discontinue the medication. In our study two women had to be given parenteral iron both belonging to the daily iron group since they experienced severe nausea and vomiting with oral iron.

Slon [21] *et al.*, Shatrugnaan [22] and Beard [23] and Souxa [24] have all corroborated the fact that increasing dose frequency also increases the side effects.

Preterm labour and low birth weight are common when Haemoglobin is less than 9gms or more than 13gms. Haemoglobin above the upper limit can give rise to decreased plasma expansion and is associated with poor pregnancy outcomes. In our study there was no preterm babies and no difference in birth weight in both groups, neither was there any growth restricted babies.

Conclusion

Intermittent dose seems convenient compared with daily dosing. There was no difference in Haemoglobin levels when administered daily or on alternate days. This regime was more cost effective and had less side effects and better compliance. Intermittent iron can also be practised for anaemic pregnant women since the absorption is better, however the improvement is better with daily iron. There is no benefit in increasing the dose to twice or thrice daily since required benefit was seen even with a daily dosing

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