ABSTRACT:
Iron deficiency has been a serious health issue especially in pregnancy. Various studies now consider daily iron as an excessive source of iron supply. In present study we compare effectiveness of daily versus weekly iron treatment. It was a randomized longitudinal study. Study included 110 pregnant anemic women attending out patient department of Gyne & Obs, CHK receiving 200 mg ferrous sulfate daily or weekly (n=55 in each group). Overall 80% patient completed the study. 76% in daily group while 83% in wkly group completed the study. Hb conc., SFC, RBC count, Red cell indices and reticulocyte count were assessed to compare the effectiveness of two regimens. Hb was determined using the cyanmethemoglobin method. SFC was determined using a commercial kit (Enzymun-Test Ferritin; Roche Diagnostics GmbH, Mannheim, Germany). Other hematological parameters were determined by using automated analyzer by Hiroshi Yamamoto, Kobe; Masanuki Oka, Kakogawa, Japan. All parameters improved significantly in women of both treatment groups. Hb% (p<0.05), RBC count (p<0.01) and Reticulocyte count (p<0.05) were significantly increased in weekly group when compared with daily group. Serum ferritin increases non-significantly in daily group when compared with weekly group (p>0.05). It was concluded that weekly supplementation of iron is equally effective in controlling IDA, when compared with daily iron supplement. A non-significant greater increase in SFC in daily group might support iron overload theory.

Keywords: Iron Deficiency Anemia, Anemia In Pregnancy, Oral Iron, Intermittent Iron Supplements, Hematological Changes

INTRODUCTION
According to estimates from the World Health Organization report, majority of women suffers from iron deficiency anemia during their pregnancy. This includes both developed and developing countries (WHO, 1992). On average 56% of pregnant women in developing countries while 18% of women from industrialized countries are anemic (WHO, 1992). Iron deficiency anemia (IDA) is a major dietary deficiency in developing countries including Pakistan (UNICEF 1994). Iron deficiency anemia can result into serious outcomes in pregnancy like maternal mortality, pre-term delivery & low birth weights (Quillan et al., 1983; Sapre and Joshi, 1996, Spinillo et al., 1994).

To control iron deficiency anemia diet modification practices and food fortification are recommended. Oral iron supplementations are required and suggested when dietary modifications are either not providing the normal requirements. Alternatively, when there is increased demand for which diet alone is not sufficient in maintaining iron stores. Although oral iron supplementation is consi-
dered to be the most effective measure to control iron deficiency anemia but studies by Wright & Southon in 1990 and Viteri et al., 1995 showed the poor compliance due to side effects of oral iron.

The prevalence of iron deficiency is much more than the prevalence of iron deficiency anemia as indicated by decrease serum ferritin and low or nearly absent stainable iron in bone marrow. It often develops during the later stages of pregnancy even in women who enter pregnancy with relatively adequate iron stores (Puolakka et al., 1980). For this reason, and due to uncertainties regarding the benefits of iron supplementation on pregnancy outcome, there is doubt about routine iron supplementation in pregnancy.

In recent years, oral iron supplementation program has been focused from daily doses to intermittent doses (once or twice weekly). The hypothesis behind intermittent iron supplementation has been based on “mucosal block” theory of iron absorption. According to this theory, down-regulation of iron absorption occurs by mucosal enterocytes when exposed to a daily high intake of iron. Mucosal ferritin synthesis increases with an increase in the enterocyte iron and a decrease in transfer of iron to blood transferrin. Studies in laboratory animals by Fairweather et al (1985), Wright & Southon in 1990 & Viteri et al (1995) indicate that the daily administration of oral iron impairs the iron absorption of the subsequent iron dose. These findings were in accordance to human studies by Fairweather & Minski (1986), ONiel & Crosby (1987) and Ridwan et al. (1996). According to the WHO (2001), iron supplement programs provide a short-term effectiveness of 70% if correctly followed. However, Pena-Rosa & Viteri (2007) and Reveiz et al (2007) have suggested that lower doses promote high effectiveness.

The aim of this study was to find out whether once weekly supplementation of oral iron would improve hemoglobin (Hb) level, serum ferritin concentration (SFC), RBC count, reticulocyte count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) as effectively as daily supplementation in pregnant women with iron deficiency anemia.

SUBJECTS AND METHODS

The study was carried out on pregnant anemic women attending the antenatal clinic of Department of Gyne & Obs, Civil Hospital, Karachi.

Subjects

According to the criteria of WHO (1992), Hb concentration of less than 11 g% during pregnancy is defined as anemia. Therefore, pregnant women with Hb value less than 11g/dl were included in the study.

Selection criteria

Inclusion criteria were singleton pregnancy, more then 12 weeks of gestation and no prior intake of iron in current pregnancy. The women with severe anemia (<7g/dl), any known hemoglobinopathy, chronic diseases of liver, cardiovascular system and kidney; medical disorders like tuberculosis, diabetes mellitus, multiple pregnancy; history of antepartum hemorrhage or intolerance to oral iron in previous pregnancies were not included in the study. Due to ethical reasons, no placebo group was included in the study.

Study design

Study was randomized, longitudinal in nature, as it compares the effect of daily iron verses intermittent (once weekly) iron supplementation before & after intervention. This study was design for 12 weeks. Sample size was calculated on the basis of 5% significance level (two-tailed test), power 80%, standard deviation 10g/dl & a difference of Hb concentration of 5g/dl. This comes out to be 42 women in each group. Keeping a drop out rate of 20% and rounding it of, 55 women in each group was required. 126 women were screened. Out of which 110 women who fulfilled the above criteria were recruited for
the study. They were randomly allocated (n=55) in each group. Randomization was performed using a random number generator.

**Group 1**: Consist of 55 women receiving 200 mg ferrous sulphate daily +500mg elemental calcium (1250mg calcium carbonate) once daily + vitamin C 500mg once daily (n=55).

**Group 2**: Consist of 55 women receiving 200 mg ferrous sulphate once weekly for 12 weeks +500mg elemental calcium (1250mg calcium carbonate) once daily + vitamin C 500mg once daily (n=55).

A detailed history was taken and a complete clinical examination was performed at the time of enrollment. General physical examination included gestational age of fetus, height, weight, body mass index (BMI) and blood pressure of mother. These physical parameters were assessed at each visit. A detailed hematological work up including hemoglobin, SFC, RBC count, Red cell indices and reticulocyte count was done.

Venous blood samples (10 ml) were collected in standard tubes containing ethylene diamine tetraacetic acid (EDTA) as anticoagulant. 5 ml was transferred in a tube for measuring Hb concentration. Hemoglobin was determined by using the cyanmethemoglobin method as mentioned by INCAG, (1985). In this procedure Hb is converted to one of its compound cyanmethemoglobin and its concentration is determined by measuring absorption at 540 nm in spectrophotometer (Model UVD-3000 Labomed, Inc. California, United States). Serum ferritin was determined using a commercial kit (Enzymun-Test Ferritin; Roche Diagnostics GmbH, Mannheim, Germany) Hematocrit, RBC count, MCH, MCHC and MCV were determined by using automated analyzer by Hiroshi Yamamoto, Kobe; Masaaki Oka, Kakogawa, Japan.

**Follow-up**

Each follow-up visit was after 4 weeks. Hence, each woman had visits after every 4 week till she completed a trial of 12 weeks. Patients were asked to report any adverse effect to oral iron therapy immediately. The blood indices were re-evaluated at each visit to observe the effect after iron supplementation. Selected physical parameters were also noted at each visit.

**STATISTICAL ANALYSIS**

Statistical analysis was done by using SPSS-10 software. The values were given as mean ± SEM. Student's t-test was used to compare between the two groups.

**RESULTS**

Initially 126 women were screened. Out of these only 110 were recruited into to 2 groups (Fig. 1). 55 women in each study group were randomly allocated. Women were enrolled between 16 and 24 weeks of pregnancy.80% (n=86) completed the study while 20% (n=22) were excluded. The reasons for exclusion were mostly due to intolerance to oral iron. 76% (n=42) of daily group while 83% (n=46) of once weekly group successfully completed the study.

The selected physical characteristics of the women in the two groups are shown in Table -I. No significant difference existed between the two groups in age, BMI and blood pressure at the start of the study.

The comparison of mean (± SEM) values of Hemoglobin, RBC count, Reticulocyte Count and RBC indices namely MCH, MCV, MCHC and SFC of both the groups were not statistically different, at the beginning of treatment. Results showed significant increments in final values of each variable in both groups. Statistically significant results after the completion of study were seen when once weekly group was compared with daily group, except for RBC indices and serum ferritin.

Mean Hb value after the treatment (Table-2) showed a greater increase in once weekly
Table-1
Selected physical parameters of women in the study. Maternal age, blood pressure and BMI at the time of enrollement in the study. Values are expressed as mean (±SEM)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Age (Yrs)</th>
<th>Blood Pressure (mmHg)</th>
<th>BMI Kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td>Daily Group (n=42)</td>
<td>24.8 ±6.2</td>
<td>111.5 ±2.18</td>
<td>69.54 ±1.86</td>
</tr>
<tr>
<td>Once weekly Group (n=46)</td>
<td>24.7 ±4.8</td>
<td>116.23 ±2.46</td>
<td>70.16 ±1.54</td>
</tr>
</tbody>
</table>

group when compared with daily group (group comparison p<0.05). Group comparison for final RBC Count & Reticulocyte count showed a significant increase (p<0.01 and p<0.05) respectively (Table-3). Reticulocyte count increases in both the groups indicating the effectiveness of both the therapeutic regimens. Final increment of two groups in MCH, MCV, MCHC (Table-3) and serum ferritin (Table-2) were non significant (p>0.05) when compared with each other. Serum ferritin (Table-2) of daily group showed a greater increase as compared to once weekly group.

Hemoglobin concentrations showed a faster increase in weekly supplementation group than in daily supplementation group (Table-4). When both the groups compared with each other at 4th, 8th and 12th weeks, results were significantly different (Fig.2). Final Hb concentrations at 12th week showed significant increment when compared with initial Hb value of that group. A greater
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**Table-2**
Mean (±SEM) Values of hemoglobin and serum ferritin of two groups (Pre and Post supplementation data)

<table>
<thead>
<tr>
<th>Hematological Parameters</th>
<th>Once Daily Group (n=42)</th>
<th>Once Weekly Group (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-Supplementation</td>
<td>Post-Supplementation</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>9.4</td>
<td>11.82</td>
</tr>
<tr>
<td>Ferritin (ug/L)</td>
<td>23.8</td>
<td>41.1</td>
</tr>
<tr>
<td></td>
<td>P value &lt;0.05</td>
<td>P value &gt;0.05</td>
</tr>
</tbody>
</table>

**Table-3**
Mean (± SEM) Values of Reticulocyte, RBC count, MCH, MCV and MCHC of two groups (Pre and Post supplementation data)

<table>
<thead>
<tr>
<th>Hematological Parameters</th>
<th>Once Daily Group (n=42)</th>
<th>Once Weekly Group (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Treatment</td>
<td>After Treatment</td>
</tr>
<tr>
<td>Reticulocyte %</td>
<td>1.54</td>
<td>3.05</td>
</tr>
<tr>
<td>RBC Count (10^6 /lL)</td>
<td>3.71</td>
<td>4.11</td>
</tr>
<tr>
<td>MCH (PG)</td>
<td>24.8</td>
<td>29.00</td>
</tr>
<tr>
<td>MCV (FL)</td>
<td>83.70</td>
<td>92.26</td>
</tr>
<tr>
<td>MCHC (G/DL)</td>
<td>29.6</td>
<td>31.65</td>
</tr>
</tbody>
</table>

*P values are calculated for final values of each parameter compared between the groups.

The increase in weekly group showed a greater trial effectiveness of weekly iron program than routine daily supplements.

**DISCUSSION**

Iron deficiency accounts a major nutritional problem in world and particularly in developing countries. Chances of developing IDA are much increased in pregnancy. This is due to increased iron requirement for developing fetus and hematological changes in mother. Recent recommendations to provide iron supplements suggest intermittent iron. A study by Cook and Reddy in 1995, determined efficiency of weekly compared to daily supplementation in adults and showed that with daily administration of iron there is 13% lower absorption compared with weekly supplementation, but the difference was not statistically significant. To increase the effectiveness of iron supplements, Viteri et al. (1995) and Ridwan et al. (1996) suggested to introduce an intermittent iron supplementation program.
In the present study, physical parameters of anemic women were same in both the group. All of these women belong to low economy group, with same dietary habits. This suggests that they might have other nutritional deficiencies. In this study more women in daily group as compared to weekly group were dropped out. Reasons for dropping out were mostly due to intolerance and hence more women in daily group faced intolerance. Initial Hb value and other RBC indices were same at the beginning of treatment. All the parameters significantly increased in the end when compared with their initial values in both the group. When final Hb value, RBC Count and Reticulocyte count of Group 1 compared with Group 2, a significant increase was observed. When RBC indices & serum ferritin of Group 1 compared with Group 2 a non-significant difference was seen. Reticulocyte count in

### Table-4

Hemoglobin concentrations at baseline and increments compared with baseline at 4th, 8th and 12th weeks of therapy.

<table>
<thead>
<tr>
<th>Time of Assessment</th>
<th>Daily Group Hb g/dl</th>
<th>Weekly Group Hb g/dl</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>9.4</td>
<td>9.38</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Increment at 4th Wk</td>
<td>0.4</td>
<td>0.5</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Increment at 8th Wk</td>
<td>1.2</td>
<td>1.5</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Increment at 12th Wk</td>
<td>2.42</td>
<td>3.33</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Final Hb at 12th Wk</td>
<td>11.82</td>
<td>12.43</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

![Fig. 2: Comparison of increments in Hb concentration of daily and weekly iron supplement groups at each visit.](image)

Increase in Hb concentration at each visit (1st visit-4th wk, 2nd visit 8th wk and 3rd visit at 12th wk).
both the treatment group effectively increased. This clearly indicates that both the treatment regimens are equally effective in treatment of IDA.

SFC values show a non-significant better response in daily iron therapy. This response is not significant enough to consider daily iron as a better treatment option in controlling IDA. This can be said because still intermittent iron is able to maintain other hematological values. Also a slow response in case of intermittent iron could justify the iron overload in daily iron doses. Our results are in accordance with Siddiqui et al (2003), Mukhopadhyay et al (2004) and Paulino et al (2005) who also favors intermittent iron supplementation in pregnancy. Present study clearly reveals that once weekly iron supplementation in pregnancy is good enough to maintain the Hb, SFC, reticulocyte count, RBC count, MCV, MCH and MCHC. All these parameters respond well to this treatment regimen. If only these parameters are concerned once weekly iron supplement is as effective as routine daily supplement.

CONCLUSION

In conclusion our study showed that in the treatment of IDA in pregnancy, intermittent iron (once weekly) regimen was comparable to daily iron supplement when given for a period of 12 weeks. In this study, only hematological parameters were considered. Hence, we cannot evaluate the oxidative stress theory in favour of intermittent iron therapy; however, a comparative little increase in SFC in presence of maintained Hb and other RBCs indices might favours an iron load in daily iron therapy. Observations of this study favours intermittent iron as an effective mode of treatment for IDA in pregnancy.

REFERENCES


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