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ORIGINAL ARTICLE

DAILY IRON SUPPLEMENTATION RESULTS IN GREATER INCREASE IN RED BLOOD CELL VOLUME WHILE INTERMITTENT IRON RESULTS IN GREATER INCREASE IN HEMOGLOBIN LEVEL IN IRON DEFICIENCY ANEMIA OF PREGNANCY

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ABSTRACT:

This study aimed to evaluate the relative effectiveness of two different oral iron regimens on hematological parameters in anemic pregnant women. Study was longitudinal & randomized .Total 160 anemic women attending outpatient clinic of a teaching hospital, were enrolled in the study. Daily group (n=80) received 200 mg ferrous sulphate daily for 12 weeks. Twice weekly group (n= 80) received 200 mg ferrous sulphate twice weekly for 12 weeks. Hemoglobin concentration (Hb conc.), Red blood cell (RBC) count, Red cell indices and reticulocyte count were assessed to compare the effectiveness of daily verses twice weekly iron supplements.

In this study 90% (n=72) women in daily and 85% (n=68) women in twice weekly group completed the study period. All parameters showed significant improvement for both treatment groups. Hb , hematocrit and RBC count showed a non significant better response in twice weekly group (P value > 0.05). Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), and reticulocyte count showed a significant better response in twice weekly group (P value <0.05). Mean corpuscular volume (MCV) showed a significant better response in daily group. From the results it can be concluded that twice weekly iron supplementation is equally effective to treat anemia during pregnancy. Daily iron results in greater increase in MCV which might be an additional cause of physiological macrocytosis.

Keywords: Iron deficiency anemia, intermittent iron, macrocytosis, oral iron, pregnancy.

INTRODUCTION

Iron-deficiency anemia is considered as the most widespread nutritional deficiency (Fauzi *et al*., 2007). It affects people of all ages and of both developed and developing countries (Bux *et al.*, 2006). Severe anemia (hemoglobin (Hb) less than 80 g/l) in the first half of pregnancy has been proved to be associated with preterm delivery and small-for-gestational-age fetus (Awan *et al*., 2004; Sheikh *et al*., 1996 and Murray *et al*., 2007). Anemia of pregnancy, directly or indirectly contributes to a significant proportion of maternal deaths as well. The national health survey of Pakistan reported that 43% to 47% rural & 35-40% urban women between 15-44 years are anemic (Mohyuddin , 1995).

Among the general measures to control iron deficiency the, oral iron supplement program is the most practical short-term approach to alleviate the problem (Mukhopaddhay *et al*., 2004). Either daily or weekly, iron supplements are required in iron deficiency anemia, as they improves in pre-term labour & birth weigh (Siega *et al*., 2006). Significantly low Hb% & packed cell volume

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(PCV) in pregnancy is due in part to dietary iron deficiency therefore iron therapy is helpful to maintain the Hb% & PCV nearer to that of non-pregnant women(Waheed *et al*., 2007). Also low serum iron & high total iron binding capacity (TIBC) in pregnant women is due to dietary iron deficiency therefore needed to be corrected with iron supplements (Waheed *et al*., 2007).

Although iron supplements are required to maintain the iron requirements of mother and her developing fetus during pregnancy, still there are some doubts about their relative benefits (Rioux and Balance 2007). To solve the problem, different doses are being in use to correct iron deficiency anemia. In recent years few clinical trials have suggested that iron supplements should not be used on daily basis. Studies have been carried out both in laboratory setups (Wright and Southron1990) and in clinical trials (Jaun *et al*., 2004 and Ridwan *et al*., 1996). These studies have concluded that with the use of iron supplementation on non daily basis, the constant gut mucosal iron load is reduced. This over load usually accompanies daily supplementation. When this burden is reduced, iron absorption occurs more efficiently and about 2.6 folds increase in absorption is seen (Viteri and Line 1995). This iron over load not only decreases iron absorption but might also be a cause of oxidative stress (Khalid and Ahmad 2012) and decreased absorption of other micro nutrients (Klevay 2001). Based on these views some studies suggest intermittent iron supplement (Rukhsana *et al*., 2006) and even suggest that weekly supplement to adolescent girls should be universally started to correct that iron stores (Deshmaka and Gang 2008).

MATERILAS AND METHODS

The study was conducted in a public sector teaching hospital of Karachi from July 2009 to February 2010. Study was randomized, longitudinal in nature which compared the hematological effects of daily and twice weekly iron supplementation program. Ethical committee approved the study as it does not included any harmful or extra surgical or medical procedures.

Selected candidates were randomly assigned to either daily or twice weekly group with the use of computer generated numbers. A sample size of 64 per group was calculated based on 5% significance level (two tailed test), with power of 80% and difference in Hb Concentration of 5g/L and standard deviation of 10g/L. With a dropout rate of 20% and rounding of the figure 80 pregnant women in each group were required.

Pregnant women, attending the outpatient department with single fetus of gestational age of 16 weeks and above with Hb value between 7g/dl to 11g/dl with no obstetric complications or any co morbidity were eligible for study. Women with history of any drug intake or iron supplements in current pregnancy or intolerant to iron supplements in any previous pregnancy were not included in the study.

Total 197 were screened out of which 80 eligible women were placed in each of the following groups.

Group 1: Consist of 80 women receiving 200 mg ferrous sulphate daily +500mg elemental calcium once daily + vitamin C 500mg once daily (n=80.)

Group 2: Consist of 80 women receiving 200 mg ferrous sulphate twice weekly +500mg elemental calcium once daily + vitamin C 500mg once daily (n=80).

At the time of enrollment detailed history was obtained. In addition a detailed general physical and clinical examination was carried out including gestational age of fetus. Gestational age was investigated by both by the date of last menstrual period and ultrasound. Other information included height, weight and blood pressure. All the women were informed and written consent was obtained for participation in the study.

Hemoglobin was determined by using the cyanmethemoglobin method as mentioned by INCAG, 1985. Serum ferritin was determined using a commercial kit (Enzymun-Test Ferritin; Roche Diagnostics GmbH, Mannheim, Germany). Hematocrit, red blood cell (RBC) count, Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC) and Mean corpuscular volume (MCV) were determined by using automated analyzer by Hiroshi Yamamoto, Kobe; Masaaki Oka, Kakogawa, Japan.

Follow up visits were planned after every 4 weeks. Total duration of study was 12 weeks. Each woman had to visit 4 times including the enrollment visit. In each follow up all the physical and clinical examinations and biochemical measurements were repeated. These women were also interviewed regarding side effects (heart burn, nausea, vomiting, diarrhoea and constipation) of iron supplements in each follow up visit. 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 AND DISCUSSION

Initially 197 women were screened. Out of these only 160 were recruited into to 2 groups (Fig.1) i.e. 80 women, each in daily and twice weekly group were allocated randomly. All over 87.5% (n=140) women completed the study. More women in daily group completed the study i.e 90% (n=72) as compared to twice weekly 85% (n=68). Reasons for not completing the study were mainly intolerance for oral iron in daily group and pregnancy induced hypertension in twice weekly group. Physical characteristics of women (Table 1) do not differ much (P value > 0.05).Hematological parameters before and after the treatment are shown in Table 2. Hemoglobin concentration and RBC indices of two groups were not much different at the beginning of therapy (P value >0.05). Although they were either at lower side of normal values or below normal limits. All these parameters showed significant improvement after the completion of therapy. These improvement were seen in both groups when pre treatment and post treatment values were compared.

Except for hematocrit (P value >0.05) all the parameters of both groups were significantly improved (P value <0.05) when compared with their pre treatment values. Hb, hematocrit and RBC count showed a non significant better response in twice weekly group (P value >0.05). MCH, MCHC and reticulocyte count showed a significant better response in twice weekly group (P value <0.05). MCV of daily group showed significantly better response (P value <0.05) when compared to twice weekly group.

Long term iron deficiency results in Iron deficiency anemia due to imbalance between iron absorption and requirements. Importance of IDA in pregnancy and its treatment has been reported widely. Iron deficiency results not only in the short term effects on mother and developing fetus but the long term effects have been reported (WHO 2002 and James *et al*., 2009). This study aims to provide data regarding effects of two different regimens oral iron on Hb concentration and erythrocyte indices during pregnancy. During pregnancy, physiological changes in hemodynamic state leads to hemodilution. Himodilution is basically due to increase in plasma volume that exceeds RBC count (Jaun *et al*.,2004). This is much evident during mid-pregnancy. This hemodilution results in decrease of Erythrocytic indices but within normal physiological limits. It has been postulated that this plasma expansion is particularly a source for better blood circulation to placenta and ultimately to fetus (Ziaei *et al*., 2007). With the improvement of Hb concentration, oxygen carrying capacity of RBCs increases and ultimately more oxygen is provided to the tissues. RBC production is stimulated by erythropoietin production. Altered oxygen supply stimulates erythropoietin from kidneys. In present study iron supplements, both daily

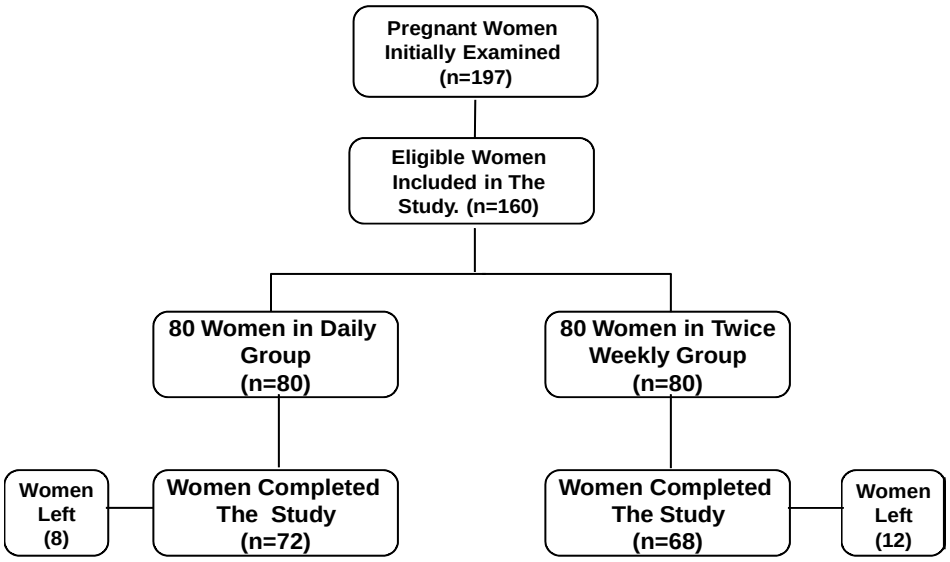

Fig. 1: Flow chart showing allocation of women in study.
Abbreviations; n = number.

Table 1
Selected Physical Parameters of Women in the Study

Groups	Age (Yrs)	Blood Pressure (mmHg)		BMI Kg/m^2	Parity	Gestational age
		Systolic	Diastolic			
Daily Group (n=42)	25.6 (±5.3)	119.6 (±2.25)	78.14 (±1.73)	22.45 (±0.39)	3.1 (±0.26)	18.5 (±0.19)
Twice weekly Group (n=46)	26.8 (±4.7)	124.13 (±2.61)	76.44 (±1.61)	21.95 (±0.37)	2.9 (±0.31)	17.9 (±0.26)

Values are expressed as Mean (±SD)

and weekly not only improved Hb concentration but also effects Erythrocytic indices. Like many previous studies this study showed physiological macrocytosis (Mukhodophaday *et al*., 2004; Taylor and Lind 1976 and Mohamed 2000). When macrocytosis is within normal physiological limits its quit safe but studies have reported that iron induced macrocytosis could result in increased blood viscosity with impaired blood perfusion of placenta . This might explain why high maternal Hb levels are related to low birth weights, preterm and small for gestational age babies (Lao *et al*.,2000 and Scanlon *et al*., 2000).

When above results are considered, intermittent iron supplementation seems to be good choice to prevent or treat anemia (Mukhodophaday *et al*., 2004; Mozaffari *et al*., 2010 and Khalid *et al*., 2011). This is also because of the cost effectiveness and much

Table 2
Hematological Parameters of Women of Both Groups at Each Visit

Hematological index		0 week	4 week	8 weeks	12 weeks
Hemoglobin	*Daily*	9.2 (± 2.1)	9.8(± 2.2)	10.4 (± 2.1)	11.92* (±2.2)
	Twice Weekly	9.31(±2.3)	10.1(± 2.1)	11.9(± 2.2)	12.24*†(±3.1)
RBC Count	*Daily*	3.61(± 0.9)	3.72(± 1.0)	3.81(± 1.2)	4.14*(± 1.3)
	Twice Weekly	3.54(± 1.2)	3.76(± 1.1)	4.11(±1.8)	4.37*†(± 1.9)
Hematocrit	*Daily*	34.1(± 2.4)	34.2(± 2.5)	34.16(± 2.8)	34.4$^{\Omega}$(± 3.8)
	Twice Weekly	34.7(± 1.9)	34.1(± 2.3)	33.5(± 2.7)	34.8 $^{\Omega}$ †(± 3.5)
MCV	*Daily*	83.68(± 3.8)	85.8(± 4.8)	88.21(± 6.9)	90.47* $^{\xi}$(± 6.5)
	Twice Weekly	84.12(± 3.7)	84.15(± 5.4)	86.78(± 6.4)	87.17 *(± 6.10)
MCH	*Daily*	26.7(± 2.0)	27.4(± 2.9)	27.6(± 2.8)	28.1*(± 2.9)
	Twice Weekly	25.54(± 1.8)	26.1(± 3.1)	28.2(± 2.4)	29.82* $^{\xi}$(± 2.8)
MCHC	*Daily*	28.5(± 2.2)	29.1(± 2.1)	30.1(± 0.8)	31.32*(± 1.1)
	Twice Weekly	29.68(± 1.9)	30.2(± 2.0)	31.4(± 1.8)	32.73* $^{\xi}$(± 2.1)
Reticulocyte Count	*Daily*	1.43(± 0.7)	1.75(± 0.7)	2.12(± 0.8)	2.9*(± 0.7)
	Twice Weekly	1.39(± 0.4)	2.12(± 0.8)	3.15(± 0.9)	3.75* $^{\xi}$(± 0.8)

* P value <0.05 When initial and final value within the group is compared
$^{\Omega}$ P value >0.05 When initial and final value within the group is compared
† P value >0.05 When final values of both groups are compared
ξ P value <0.05 When final values of both groups are compared

fewer side effects when compared to daily supplementation programs (Deshmka and Gang 2008 and Souza *et al*., 2009).

Results of present study favours intermittent iron supplementation not only on the basis of Hb value but has considered RBC indices for the effectiveness of treatment regimen.

Limitations of study were use of oral iron only and the fact that only urban population with non vegetarian diet were recruited for the study. Also folic acid supplementation was not included in the trial which might results in macrocytosis as data shows that folate anemias and mixed anemias are still seen in pregnant women (Bux *et al*., 2003).

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