Effectiveness of twice weekly iron supplementation compared with daily regimen in reducing anemia and iron deficiency during pregnancy: A randomized trial in Iran

Article *in* Journal of research in medical sciences · September 2008

Source: DOAJ

CITATIONS
8

READS
477

5 authors, including:

Ahmadreza Zamani
Isfahan University of Medical Sciences
21 PUBLICATIONS **232** CITATIONS
SEE PROFILE

Ziba Farajzadegan
Isfahan University of Medical Sciences
191 PUBLICATIONS **1,305** CITATIONS
SEE PROFILE

Attaollah Ghahiri
Isfahan University of Medical Sciences
30 PUBLICATIONS **208** CITATIONS
SEE PROFILE

Mohammad Khademloo
Mazandaran University of Medical Sciences
69 PUBLICATIONS **412** CITATIONS
SEE PROFILE

Received: 27.1.2008 **Accepted: 28.4.2008**

Original Article

Effectiveness of twice weekly iron supplementation compared with daily regimen in reducing anemia and iron deficiency during pregnancy: a randomized trial in Iran

Ahmad Reza Zamani, Ziba Farajzadegan*, Ataollah Ghahiri**, Mohammad Khademloo***, Parastoo Golshiri*****

Abstract

BACKGROUND: Over 40 millions pregnant women are suffering from iron deficiency (ID) and it's consequences in developing countries presently. If the effects of twice weekly iron supplementation on hemoglobin (Hb) and serum ferritin (SF) to be shown comparable to daily iron supplementation in pregnancy, it will reduce the cost, will diminish the side effects, will increase the compliance and will prevent the potential harmful effects of extra iron supplement.

METHODS: A total of 152 pregnant women were enrolled in the study in two different clinics in Isfahan, Iran. The inclusion criteria were 2nd trimester pregnant women aged between 18-38 years with the initial Hb ≥ 110 g/L. They were randomized into two treatment groups, either the twice weekly (TW) taking iron group (two 45-mg ferrous sulfate tablets per week) or daily taking iron group (45 mg ferrous sulfate tablet). The age, weight, education and employment status of pregnant women along with their parity distributions and gestational age at onset of treatment in the two groups were comparable. Sixty nine and fifty three pregnant women of daily group and TW group, respectively, could be followed up regularly at 4 weekly intervals until 16 weeks of supplementation. Side effects, compliance and the number of tablets consumed were noted for each group. Blood was sampled at 15-16 and 37-39 weeks of pregnancy and blood indices were evaluated to see the effect of iron supplementation.

RESULTS: The mean initial Hb concentrations were 133 ± 11 g/L and 130 ± 12 g/L in daily and TW groups, respectively, which were not significant. The mean final Hb concentrations were 127 ± 15 g/L in daily group and 120 ± 13 g/L in TW group ($p < 0.05$). The decrease of Hb from the start to the end of therapy was significant in both groups and the decrements significantly were less in daily group. The SF increased non-significantly in daily group and decreased non-significantly in TW group but, there was no difference in ferritin values of the two groups at near term.

CONCLUSIONS: Daily regimen was more effective than TW regimen in preventing Hb decrement at near term in our study.

KEY WORDS: Pregnancy, anemia, iron deficiency, hemoglobin, ferritin, developing countries, iron supplementation.

JRMS 2008; 13(5): 230-239

Considering the facts that: 1- more than 240 millions of the world's population were females of 15 to 19 years living in developing countries in 2002[1]; 2- seven percent of them give birth in one year[2]; 3- the prevalence of anemia among pregnant women averages 56%, ranging between 35 to 100% in developing countries[3,4] and 4- more than 85%

*Assistant Professor, Community Medicine Department, Isfahan University of Medical Sciences, Isfahan, Iran.
**Associate Professor, Obstetric and Gynecologic Department, Isfahan University of Medical Sciences, Isfahan, Iran.
***Assistant Professor, Community Medicine Department, Sari University of Medical Sciences, Sari, Iran.
****Assistant Professor, Public Health School, Isfahan University of Medical Sciences, Isfahan, Iran.
Correspondence to: Dr Ahmad Reza Zamani, Community Medicine Department, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: zamani@med.mui.ac.ir.

of the nutritional anemias are iron deficiency anemia (IDA) alone, or of iron combined with folate or other nutrient deficiencies,[2,5] lead us to the conclusion that at the moment you are reading these lines, close to 8 millions pregnant teens aged 15-19 years are suffering from iron deficiency (ID) and it's consequences just in developing countries. If we add females aged 20-44 years (over 940 millions in 2002), the suffering population percentage is to be multiplied at least by 5 in developing countries presently. UNICEF has reported deaths of an estimated 50,000 young women per year globally in pregnancy and childbirth due to severe iron deficiency anemia.[6] The etiology of anemia in developing countries is multifactorial; poor bioavailability of dietary iron, malaria, chronic inflammation, hemoglobinopathies, intestinal parasitic infections, micronutrient deficiencies specially folate, zinc, riboflavin or vitamin A, lack of education, frequent and closely spaced pregnancies and socioeconomic deprivation are among the most common ones.[7-10] The resultant anemia can distress both baby and mother; from fetal morbidity to preterm delivery in baby and from prolonged postpartum depression to increased maternal mortality in mother.[4,11] Indices of erythrocytes change in pregnant women, largely due to hemodilution and iron-deficient erythropoiesis. Some studies have shown that the best outcome conditions including birth weight, delivery time, and maternal health, happens when the Hb concentration at term is between 95 and 125 g/L.[12,13] Different authors argue that iron needs during pregnancy range from 450 to 1150 mg with a median of 790 mg; since these requirements are difficult to meet through an ordinary diet, specially in developing countries in which most diets do not contain enough bio-available iron, it seems that routine iron supplementation in pregnant women is a must in almost all patients.[14-17] In Iran, it is mandatory to prescribe iron (one 45 mg ferrous sulfate tablet per day) and folic acid supplements to pregnant women after the 15th-18th week of gestation; however, problems of non-compliance with oral iron supplements are well-recognized here too.[18] Several attempts throughout the world have been made to overcome the non-compliance including weekly or TW administration of oral iron supplements.[19] The latter approach was initiated based on the experimental evidence that the iron absorption is reduced in rats in the days immediately after the initial administration of a large dose of iron but is resumed after < 3 days[20,21] and that the side effects limits the compliance.[22] We decided to evaluate the relative effectiveness of TW iron supplementation on some hematological indicators and iron deficiency at term compared with ongoing national daily iron supplementation program in pregnancy.

Methods

Ethical Considerations

The ethics committee of the research department of medical faculty of Isfahan University of Medical Sciences approved the study protocol. The purpose of the study was explained and a verbal consent was taken from all the subjects.

Study Population, Enrollment and Sample Size

All healthy pregnant women 18-38 years of age attending prenatal care at the Haftoon clinic and Ghahiri clinic, Isfahan, Iran, who had than 17 weeks of gestational age were invited to participate in this field-based randomized trial. They were not admitted to the study if any of the following criteria were present: current anemia (Hb < 110 g/L), past history of anemia, thalassemia or any other blood disorders, a past or present obstetrical history of hemorrhage, pregnancy induced hypertension and/or diabetes and those who were suffering from any chronic systemic disorder. Body weight and gestational age were measured at baseline (week 15-16 of pregnancy) and at near-term assessments (week 37-39 of pregnancy). Gestational age was estimated clinically (by palpation and from the last menstruation period) and using ultrasound, which later was adjusted by delivery date. Demographic characteristics and past obstetric history were as-

sessed through questionnaire-based interviews. Estimated sample size indicated that 63 subjects per group were required to be able to detect a difference between groups in Hb of 5 g/L and a standard deviation of 10 g/L based on 5% significance level and power 80%. Considering a dropout rate of 20%, we planned to recruit 151 women.

Randomization and Intervention

Eligible participants were randomly assigned to control group or trial group using a computer generated numbers. Women in the control group were guided to take one 45 mg ferrous sulfate tablet daily and supplied with 28 tablets for every 4 weeks for 16 weeks in total, free of charge. Iron tablets didn't include folic acid or any other micronutrient. Women in the trial group were instructed to choose any day of the week and to take two tablets of 45 mg ferrous sulfate on the same day every week, one in the morning and the other before dinner; i.e., 90 mg of elemental iron as ferrous sulfate one day per week in two takes. They were supplied with 8 tablets for every 4 weeks for 16 weeks in total. No tablets were given for the rest of the week. One iron preparation was used for both groups and the appearance of the tablets of the two groups was identical placed in coded vials. The investigators were blind to the allocation of treatment group (daily vs. TW) at initial recruitment. Laboratory technicians were not aware of the group to which the sample was allocated too. A diary card provided for each subject to record the date of taking tablet and any symptom perceived by the women during the day, without making reference to supplement intake and therefore attributable or not to iron supplements. Mothers were followed up regularly at 4 weekly intervals until 16 weeks of supplementation. Compliance of tablet intake throughout the 16-week period and also side effects were assessed again through interview. The total number of tablets consumed during the pregnancy, the period of gestation at delivery and the mode of delivery were recorded. Blinding during follow up visits was impossible due to the nature of study.

Hb and Serum Ferritin (SF) Measurements

Venous blood samples from women were drawn at the two laboratories cooperating with clinics at baseline during gestational week 15-16 and then, at gestational week 37-39 (near term). An identical validated protocol was provided by the two laboratories cooperating with clinics to confirm the validity and reliability of the laboratory measurements. One technician from each laboratory was appointed to do the measurements. Blood samples from every 10th woman were distributed into three tubes and analyzed by a different technician and by the other laboratory to evaluate the reliability of laboratories and laboratory technician. Five ml blood was drawn into EDTA-containing tubes. A complete blood count, including Hb and hematocrit, platelets, mean corpuscular volume, mean corpuscular Hb, mean corpuscular Hb concentration was performed using Coulter Sysmex K1000 in both laboratories. The validity and reliability of both coulters were evaluated in a pilot study. Determination of SF was performed following the recommendations of the International Committee for Standardization in Hematology.[23]

Statistical Analyses

In order to reach the answer of research question, daily group was compared with the TW group based on per-protocol analysis. All quantitative variables were found to be normally distributed both before and after supplementation except SF. Since there is a physiological "U" hemodilution during pregnancy, Hb values were adjusted by gestational age and are presented as means (g/L) ± standard deviation (SD). The independent *t* test was used to test the difference between groups. To test the difference between baseline and near-term examination, the paired *t* test was applied for continuous data. Mann-Whitney test was used to compare initial and final SF values and since the results were not

different than parametric tests, SF values are reported as means ± SD (g/L) too. Pearson correlation coefficients were calculated for relationships between continuous variables. The chi-square test was used for categorical variables. Significant differences in demographic characteristics and other characteristics across groups (dropouts and stay-ins) were assessed using ANOVA. Multiple regression analysis was used to assess the effects of the treatments after adjusting for different confounding variables such as gestational age, socioeconomic characteristics, age, and initial Hb and SF value. P values < 0.05 were considered significant.

Results

A total of 180 women were invited and screened; 152 of whom were eligible and enrolled in the study. All participants had a gestational age of 15-16 wk; 72 mothers in clinic 1 and 80 ones in clinic 2 were randomly assigned to the daily supplement group and TW supplement group. One hundred twenty two women (80.26%) completed the study protocol (figure 1); 34 and 35 women in daily group in clinic 1 and 2, respectively; 23 and 30 mothers in TW group in clinics 1 and 2, respectively. Dropout subjects' hematological values and their baseline features did not differ from the stay-in women either in the daily or TW groups. Other characteristics of the women who completed the study in both clinics and in both groups are shown in table 1. At baseline, there were no significant differences between the daily group and TW group in weight, age, parity, fundal height, education or employment status. Thus, the trial effectiveness analysis could not have been confounded by these factors. Data of each group and each clinic calculated both separately and when were pooled (table 2). Iron status (Hb and SF) did not differ between daily group and TW group at baseline, whether in each clinic or pooled data (table 2).

Hb Changes

After 16 weeks of supplementation, the near term Hb values decreased significantly in both groups and the decrements also were significantly smaller with the daily regimen (6 g/L) compared with TW regimen (10 g/L). The prevalence of anemia at near term examination was non-significantly lower in daily group (3/69 or 4.3%) compared with TW group (6/53 or 11.3%). As part of inclusion criteria, none of the subjects had initial Hb concentration less than 110 g/L but, out of these 9 mothers, 2 in each group had initial SF less than 12 g/L while for final SF the number of patients changed to 1 and 3 in daily and TW groups, respectively. The risk of developing anemia was possibly higher in TW group (odds ratio 3.3, 95% CI 0.8-13.7, p = 0.08). The final Hb values of 32 women (46.4%) in daily group and 38 ones (71.7%) in TW group were fit between 95 and 125 g/L (table 3). The difference between their mean final Hb concentrations was significant (119 g/L vs. 114 g/L in respective subgroups) while in both subgroups (32 in daily vs. 38 in TW) they had the same initial mean Hb values (128.5 g/L). The difference in mean SF concentrations of the two subgroups was not significant, whether at the start of study (28.7 vs. 26.5 g/L in respective subgroups) or at the end (20.8 g/L vs. 20.2 g/L in the respective subgroups). On the other hand, initial Hb concentrations of 16 women (23.2%) in daily group and 26 ones (47.2%) in TW group were between 95-125 g/L. Both subgroups (16 in daily vs. 26 in TW) had the same initial mean Hb concentration (120.5 g/L) and the difference between their mean final Hb concentrations was not significant too (119 vs. 116 in the respective subgroups). Also, the difference in mean SF values of these two subgroups was not significant, whether at the start of study (23.1 vs. 24.7 g/L in respective subgroups) or at the end (22.4 vs. 30.1 g/L in the respective subgroups).

SF Changes

The picture of SF changes was more complex; while at near term, the mean SF concentrations increased in daily group, it showed decrements in TW group, both non-significantly (table 2). Prevalence of iron deficiency (ID), SF < 12 g/L, at baseline was 15/69 (21.75%) and

16/53 (30.2%) in daily (9 ± 2.4 g/L) and TW (10.3 ± 1.4 g/L) groups, respectively. The difference was not significant between the two groups. On the other hand, at the end of study ID was seen in 7.2% (5/69) of the women in daily group and 20.7% (11/53) of mothers in TW group. The risk of developing ID was significantly higher in TW (odds ratio 3.3, 95% CI 1.1-10.3, p = 0.03). We divided each group into 4 categories based on SF cutoff point of 20 g/L and compared their difference at baseline and at the end of study (table 4).

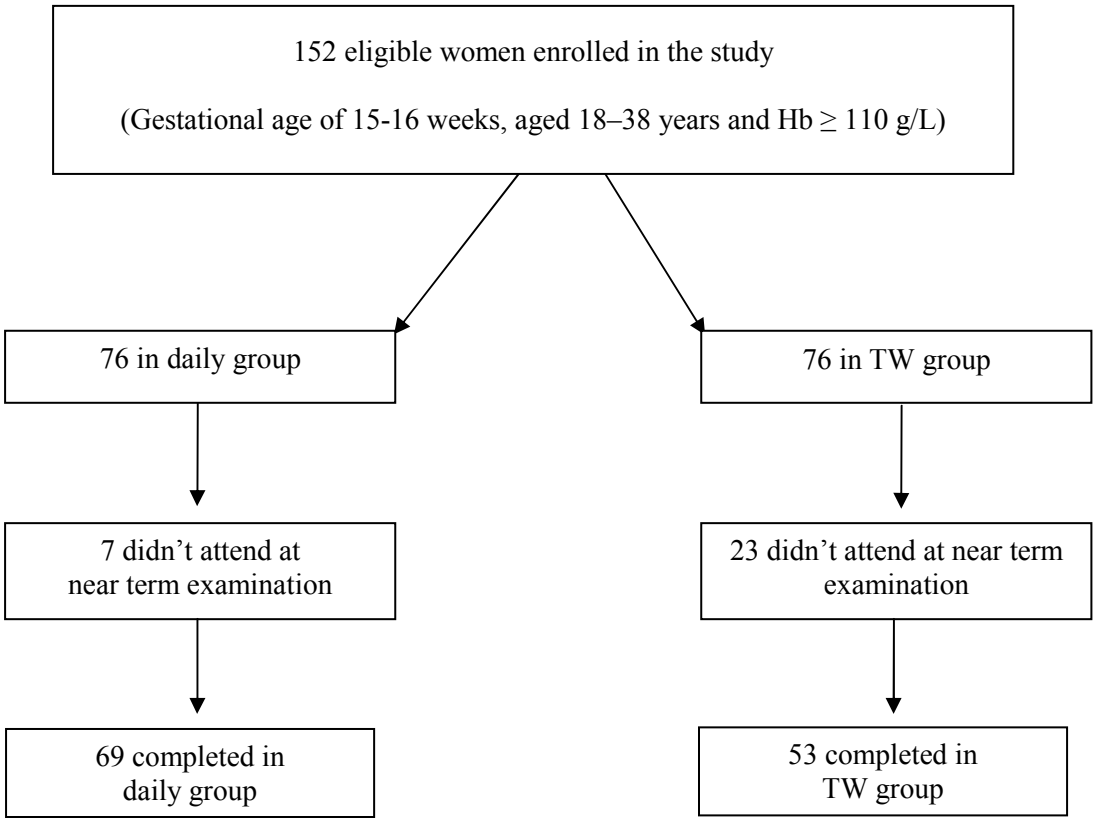

Figure 1. A total of 122 women completed the study protocol.

Table 1. Baseline characteristics of the women who completed the study in both clinics and in both groups.

Baseline Characteristics		Clinic		Iron Supplement Group	
		# 1	# 2	Daily (69)	TW (53)
Literacy (# of Mothers)	College or University	3	32	17	18
	High School Diploma	22	31	32	21
	< High School	32	2	20	14
Parity (# of Mothers)	1st Pregnancy	24	37	35	26
	≥2nd Pregnancy	19	21	23	17
Employed Subjects (# of Mothers)		3	23	13	13
Mean Age ± SD (years)		25.6 ± 5.9	26.7±4.5	25.9 ± 4.9	26.5 ± 5.7
Mean Weight ± SD (kg, before trial)		62.8± 12.2	65.9 ±13	65.3 ±11.7	63.3 ± 13.9

Table 2. Mean SF and mean Hb concentrations in both groups before and after intervention.

	Mean Hb ± SD (g/L)		Within Group P	Mean SF ± SD (g/L)		Within Group P
	Baseline	Near Term		Baseline	Near Term	
Daily	133 ± 11	127 ± 15	0.004	24.1 ± 22.9	31.6 ± 22.5	0.057
TW	130 ± 12	120 ± 13	0	29.5 ± 24.7	26.4 ±18.2	0.4
Between Groups P	0.2	0.01		0.2	0.2	

Table 3. Distribution of subjects with different concentrations of Hb at baseline and near term in both groups and in both clinics.

Hemoglobin (g/L)	Number of Subjects							
	Baseline				Near Term			
	Daily	TW	Clinic # 1	Clinic # 2	Daily	TW	Clinic # 1	Clinic # 2
<95	0	0	0	0	2	0	0	2
95-99	0	0	0	0	0	0	0	0
100-104	0	0	0	0	0	4	1	3
105-125	16	25	17	24	32	34	22	44
126-130	11	8	9	10	14	8	12	10
131-140	27	9	17	19	12	3	10	5
141-150	12	8	8	12	3	2	5	0
151-160	2	2	4	0	5	0	4	1
>160	1	1	2	0	1	2	3	0
Total	69	53	57	65	69	53	57	65

Table 4. Frequency of subjects and mean SF in 4 categories formed by considering SF cutoff point of 20 g/L in both groups before and after intervention.

SF Concentrations	Daily Group (53 women)			TW Group (69 women)			Between Groups P	
	# of Subjects	Mean SF (g/L)		# of Subjects	Mean SF (g/L)			
		Initially	Finally		Initially	Finally	Initially	Finally
Initially and Finally ≤ 20	23	10.8 ± 4	13.4 ± 5	20	11.8 ± 3	13.7 ± 4	0.4	0.9
		Within Group P = 0.02			Within Group P = 0.1			
Initially ≤20 & Finally >20	26	14.1 ± 2	46.4 ±24	11	12.5 ± 2	42.2 ± 14	0.04	0.6
		Within Group P = 0			Within Group P = 0			
Initially >20 & Finally ≤20	7	52 ± 28	15.9 ± 2	9	40.8 ± 20	12.9 ± 3	0.4	0.06
		Within Group P = 0.02			Within Group P= 0.004			
Initially and Finally >20	13	50.4±28	42.7±17	13	55.7 ± 18	43.4 ± 17	0.6	0.9
		Within Group P = 0.4			Within Group P = 0.2			

Other Measurements

Reported symptoms during the study period, not necessarily attributable to the intake of iron tablets were anorexia, fatigue, constipation, headache, nausea, vomiting and abdominal pain, which showed no significant difference between the two groups. While full compliance with iron supplementation based on diary cards was more than 90% in both groups, at the final interview only 60% of women in daily group and close to 70% in TW group verbally confirmed full compliance. Surprisingly, education background of mothers had significant negative effects on both Hb and SF concentrations; i.e., the higher the education level, the lower the final Hb and SF values at the end. Also, employed mothers had significantly lower final Hb concentration but final SF values were not affected by employment. Worthy of noting that higher education and employment both had negative correlation with initial SF concentrations but not with initial Hb values. Other baseline features had no relation to Hb and SF concentrations

Discussion

The study population consisted of a blend of high and low socioeconomic pregnant non-anemic women who were self-selected attending two antenatal clinics to evaluate the trial effectiveness of iron supplementation regimens. Due to a successful randomization, and since the dropouts characteristics didn't differ in the two groups, they remained comparable throughout the study. No maternal or perinatal consequences were reported. Despite large variations in Hb concentrations in the two clinics, they roughly followed the SF values in two groups in both clinics. The final Hb concentration depends on the iron absorption which is further dependent on the initial Hb value and pregnancy trimester. It is apparent that Hb and SF concentrations will be reduced during pregnancy even in iron-replete women[16] as it happened in our study. The women in the daily group were prescribed exactly 3.5 times of the amount of iron prescribed to the women in the TW group during 16 weeks of supplementation (5040 mg vs. 1440 mg totally in respective groups) and they performed better in preventing low iron stores, mainly on the basis of changes in values of Hb and SF; i.e., 7 g/L and 5 g/L higher final Hb and SF concentrations, respectively, associated with daily administration of iron. On the other hand, if 10% of the prescribed iron was absorbed in the 2nd trimester and 15% of that in the third trimester, roughly 180 mg of iron would have been absorbed over 16 weeks of supplementation in the TW iron group.[16,24,25] Given differential compliance between daily and TW groups, those in daily group would have at least absorbed more than double the amounts of iron absorbed in TW group and at the end:

Mean Hb decrement was significantly smaller with the daily regimen (6 g/L) compared with TW regimen (10 g/L).

The number of iron deficient mothers who showed improvement in iron status in daily group was double the number of that in TW group (10 women vs. 5 ones, respectively).

The number of iron deficient mothers in daily regimen was half of that in TW regimen (5 subjects in daily group vs. 11 ones in TW group) and the risk of developing ID was triple in the latter group.

The number of anemic mothers in daily group was half of that in TW group (3 mothers vs. 6 ones in respective groups).

The number of mothers who had initial SF value ≤ 20 g/L and final SF value > 20g/L in daily regimen was more than double the number of that in the other group (26 women vs. 11 ones, respectively).

On the other hand, the TW regimen clearly showed superior effect on SF concentrations of iron deficient mothers. More over, the risk of developing Hb > 130 g/L was almost triple of that in daily group. The latter results raise doubts about the optimum effects of daily regimen on iron indices in pregnancy.

A recently published systematic review found no differences in most pregnancy outcomes between daily and weekly iron supplementation regimens. Different trials conducted using weekly or TW iron supplementation in

pregnancy have shown a number of advantages over daily regimen, including lower cost and better compliance to supplementation[19,26-28] and similar effectiveness to daily regimen for prophylaxis in non-anemic pregnant women[28-34] or in treating anemia among pregnant women.[30,31,33] Others have shown a greater impact of daily administration on body iron than weekly or twice-weekly supplementations.[35-37] Also, some researchers believe both daily and weekly or TW iron supplementation are relatively unsuccessful in the reduction of anemia prevalence during pregnancy[34] and more attention should be paid on adolescent girls and women of reproductive age long before pregnancy through intermittent low-dose iron supplements and in some cases with necessary micronutrients[38] or through iron fortification programs[16,38] to yield the most cost effective benefits in the long term. It seems many factors other than iron and it's supplementation method, are contributing in diverse results of various iron administration programs during pregnancy including: presence of other limiting factors such as vitamin A deficiency and/or other risk factors of anemia in developing countries mentioned above,[7-10] short term administration conducted in essentially iron-normal populations or low prevalent iron deficient populations,[24,26,38] variable iron balance at different stages of pregnancy and the difficulties of correction of anemia during pregnancy,[16,38] too high concentrations set for the cutoff points of true gestational anemia by WHO,[38-40] and finally non-compliance due to lack of motivation (of both mothers and health personnel) and/or poor access to health services (lack of political commitment and financial support) and also patient factors including misunderstanding instructions, frustration about the frequency and number of pills taken, migration, fear of having big babies, personal problems, nausea that accompanies pregnancy, the subtlety of anemia which makes demand for treatment low and iron side effects.[22,41,42] Since the side effects are dose-dependent, the iron dose and frequency should be kept as low as possible that is well-matched with both unimpaired efficacy and minimum risk of hemoconcentration and it's consequences such as higher liver iron than normal which is associated with oxidative stress[20,43,44] and increased plasma free reactive iron and high ethane production occurring after ingestion of daily iron.[38,45]

Conclusions

In conclusion, our study showed that the old is still new; i.e. in non-anemic pregnant women, the intake of 45 mg iron compared with TW taking tablet starting at week 16 for a period of 16 weeks more effectively prevented Hb decrement at near term. But, since the results were suboptimal, prenatal iron supplements need to be considered individually in a flexible approach based on socioeconomic status of patients, stage of pregnancy and total iron requirements anchored in regular iron tablet ingestion. Moreover, in order to prevent the potential harmful effects of extra iron supplements, other options such as combination of daily (for the first 10 [24] to 40 [26] doses of iron to correct an existing deficit) and weekly (for maintenance after the first 10 to 40 days) administration of iron during pregnancy should be evaluated.

Acknowledgement

We would like to express our gratitude to Dr Gholam Hossein Sadri, Shahla Shahidi, Dr Ali Ajami, Nadia Rahimi, Shekoofeh Shabanian and Foroogh Aghashahi who helped us in different stages of data gathering. Also, thanks to Dr Abbas Esmaeili for helping in analysis and article editing. Finally, we appreciate all women who participated in the study.

References

1. U.S. Census Bureau. **Global Population Profile: 2002.** 3-3-2004. U.S. Government Printing Office. Washington, DC; March 2004.
2. Ashford L, Clifton D. **Women of our world**. *Population reference bureau.* 2-2-2005.
3. Brabin BJ. **An analysis of malaria in pregnancy in Africa.** *Bull World Health Organ* 1983; 61: 1005-16.
4. Allen LH. **Anemia and iron deficiency: effects on pregnancy outcome.** *Am J Clin Nutr* 2000; 71: 1280S-4S.
5. Viteri FE. **A new concept in the control of iron deficiency: community-based preventive supplementation of at-risk groups by the weekly intake of iron supplements.** *Biomed Environ Sci* 1998; 11: 46-60.
6. Hussar DA. **New drugs: pregabalin and omega-3-acid ethyl esters.** *J Am Pharm Assoc (Wash DC)* 2005; 45: 765-7.
7. van den Broek NR, Letsky EA. **Etiology of anemia in pregnancy in south Malawi.** *Am J Clin Nutr* 2000; 72: 247S-56S.
8. Bondevik GT, Eskeland B, Ulvik RJ, Ulstein M, Lie RT, Schneede J *et al*. **Anaemia in pregnancy: possible causes and risk factors in Nepali women.** *Eur J Clin Nutr* 2000; 54: 3-8.
9. van den BN. **The aetiology of anaemia in pregnancy in West Africa.** *Trop Doct* 1996; 26: 5-7.
10. van den BN. **Anaemia in pregnancy in developing countries.** *Br J Obstet Gynaecol* 1998; 105: 385-90.
11. Beard JL, Hendricks MK, Perez EM, Murray-Kolb LE, Berg A, Vernon-Feagans L *et al*. **Maternal iron deficiency anemia affects postpartum emotions and cognition.** *J Nutr* 2005; 135: 267-72.
12. Steer PJ. **Maternal hemoglobin concentration and birth weight.** *Am J Clin Nutr* 2000; 71: 1285S-7S.
13. Zhou LM, Yang WW, Hua JZ, Deng CQ, Tao X, Stoltzfus RJ. **Relation of hemoglobin measured at different times in pregnancy to preterm birth and low birth weight in Shanghai, China.** *Am J Epidemiol* 1998; 148: 998-1006.
14. Milman N, Bergholt T, Eriksen L, Byg KE, Graudal N, Pedersen P *et al*. **Iron prophylaxis during pregnancy -- how much iron is needed? A randomized dose- response study of 20-80 mg ferrous iron daily in pregnant women.** *Acta Obstet Gynecol Scand* 2005; 84: 238-47.
15. Milman N. **Serum ferritin in Danes: studies of iron status from infancy to old age, during blood donation and pregnancy.** *Int J Hematol* 1996; 63: 103-35.
16. Bothwell TH. **Iron requirements in pregnancy and strategies to meet them.** *Am J Clin Nutr* 2000; 72: 257S-64S.
17. Bodnar LM, Cogswell ME, Scanlon KS. **Low income postpartum women are at risk of iron deficiency.** *J Nutr* 2002; 132: 2298-302.
18. Kianfar H, Kimiagar M, Ghaffarpour M. **Effect of daily and intermittent iron supplementation on iron status of high school girls.** *Int J Vitam Nutr Res* 2000; 70: 172-7.
19. Hyder SM, Persson LA, Chowdhury AM, Ekstrom EC. **Do side-effects reduce compliance to iron supplementation? A study of daily- and weekly-dose regimens in pregnancy.** *J Health Popul Nutr* 2002; 20: 175-9.
20. Walter PB, Knutson MD, Paler-Martinez A, Lee S, Xu Y, Viteri FE *et al*. **Iron deficiency and iron excess damage mitochondria and mitochondrial DNA in rats.** *Proc Natl Acad Sci U S A* 2002; 99: 2264-9.
21. Knutson MD, Walter PB, Ames BN, Viteri FE. **Both iron deficiency and daily iron supplements increase lipid peroxidation in rats.** *J Nutr* 2000; 130: 621-8.
22. Galloway R, McGuire J. **Determinants of compliance with iron supplementation: supplies, side effects, or psychology?** *Soc Sci Med* 1994; 39: 381-90.
23. International Committee for Standardization in Haematology (Expert Panel on Iron). **Proposed international standard of human ferritin for the serum ferritin assay.** *Br J Haematol* 1985; 61: 61-3.
24. Hallberg L. **Combating iron deficiency: daily administration of iron is far superior to weekly administration.** *Am J Clin Nutr* 1998; 68: 213-7.
25. Svanberg B, Arvidsson B, Norrby A, Rybo G, Solvell L. **Absorption of supplemental iron during pregnancy - a longitudinal study with repeated bone-marrow studies and absorption measurements.** *Acta Obstet Gynecol Scand Suppl* 1975; 87-108.
26. Ekstrom EC, Hyder SM, Chowdhury AM, Chowdhury SA, Lonnerdal B, Habicht JP *et al*. **Efficacy and trial effectiveness of weekly and daily iron supplementation among pregnant women in rural Bangladesh: disentangling the issues.** *Am J Clin Nutr* 2002; 76: 1392-1400.
27. Liu XN, Liu PY. **The effectiveness of weekly iron supplementation regimen in improving the iron status of Chinese children and pregnant women.** *Biomed Environ Sci* 1996; 9: 341-7.
28. 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: 409-17.

29. Berger J, Thanh HT, Cavalli-Sforza T, Smitasiri S, Khan NC, Milani S *et al*. **Community mobilization and social marketing to promote weekly iron-folic acid supplementation in women of reproductive age in Vietnam: impact on anemia and iron status.** *Nutr Rev* 2005; 63: S95-108.
30. Gomber S, Agarwal KN, Mahajan C, Agarwal N. **Impact of daily versus weekly hematinic supplementation on anemia in pregnant women.** *Indian Pediatr* 2002; 39: 339-46.
31. Muslimatun S, Schmidt MK, Schultink W, West CE, Hautvast JA, Gross R *et al*. **Weekly supplementation with iron and vitamin A during pregnancy increases hemoglobin concentration but decreases serum ferritin concentration in Indonesian pregnant women.** *J Nutr* 2001; 131: 85-90.
32. Paulino LS, Angeles-Agdeppa I, Etorma UM, Ramos AC, Cavalli-Sforza T. **Weekly iron-folic acid supplementation to improve iron status and prevent pregnancy anemia in Filipino women of reproductive age: the Philippine experience through government and private partnership.** *Nutr Rev* 2005; 63: S109-15.
33. 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: 884-90.
34. Young MW, Lupafya E, Kapenda E, Bobrow EA. **The effectiveness of weekly iron supplementation in pregnant women of rural northern Malawi.** *Trop Doct* 2000; 30: 84-8.
35. de Souza AI, Batista FM, Ferreira LO, Figueiroa JN. **[The effectiveness of three regimens using ferrous sulfate to treat anemia in pregnant women].** *Rev Panam Salud Publica* 2004; 15: 313-9.
36. Goonewardene M, Liyanage C, Fernando R. **Intermittent oral iron supplementation during pregnancy.** *Ceylon Med J* 2001; 46: 132-5.
37. Mumtaz Z, Shahab S, Butt N, Rab 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: 2697-02.
38. Viteri FE, Berger J. **Importance of pre-pregnancy and pregnancy iron status: can long-term weekly preventive iron and folic acid supplementation achieve desirable and safe status?** *Nutr Rev* 2005; 63: S65-76.
39. Rasmussen K. **Is There a Causal Relationship between Iron Deficiency or Iron-Deficiency Anemia and Weight at Birth, Length of Gestation and Perinatal Mortality?** *J Nutr* 2001; 131: 590S-601S.
40. Scholl TO, Hediger ML. **Anemia and iron-deficiency anemia: compilation of data on pregnancy outcome.** *Am J Clin Nutr* 1994; 59: 492S-500S.
41. Zavaleta N, Caulfield LE, Garcia T. **Changes in iron status during pregnancy in Peruvian women receiving prenatal iron and folic acid supplements with or without zinc.** *Am J Clin Nutr* 2000; 71: 956-61.
42. Galloway R, McGuire J. **Daily versus weekly: how many iron pills do pregnant women need?** *Nutr Rev* 1996; 54: 318-23.
43. Srigiridhar K, Nair KM. **Iron-deficient intestine is more susceptible to peroxidative damage during iron supplementation in rats.** *Free Radic Biol Med* 1998; 25: 660-5.
44. Srigiridhar K, Nair KM, Subramanian R, Singotamu L. **Oral repletion of iron induces free radical mediated alterations in the gastrointestinal tract of rat.** *Mol Cell Biochem* 2001; 219: 91-8.
45. Breuer W, Ronson A, Slotki IN, Abramov A, Hershko C, Cabantchik ZI. **The assessment of serum nontransferrin-bound iron in chelation therapy and iron supplementation.** *Blood* 2000; 95: 2975-82.