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Comparison of effect of daily versus weekly iron supplementation during pregnancy on lipid peroxidation

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Abstract

Objectives: To compare the effect of daily versus weekly iron supplementation on lipid peroxidation, hemoglobin levels and maternal and perinatal outcome in non-anemic pregnant women.

Methods: Of 109 women randomly allocated into three groups, 90 completed the study. Group I ($n = 30$) received daily iron folic acid; Group II ($n = 30$) received weekly iron folic acid; Group III ($n = 30$) received daily iron (III)-hydroxide polymaltose complex. Hemoglobin levels, hematological indices, thiobarbituric acid reactive substances (TBARS) and glutathione levels were measured at baseline (14–16 weeks) and at 30–34 weeks. Statistical analysis was done using the ANOVA test.

Results: Group I had a highly significant increase in TBARS level (0.61 ± 0.26 μmol/L, $P = 0.000$) compared to groups II and III in which the change in TBARS was not significant (0.02 ± 0.06 and 0.007 ± 0.06 μmol/L, respectively). There was an insignificant fall in glutathione levels in all groups. There was no significant difference in the mean period of gestation, pregnancy complications and neonatal outcome between the three groups. Among 22.2% of women who were non-compliant, Group I had significantly higher incidence of non-compliance ($P = 0.016$) and side-effects ($P = 0.001$). Final hemoglobin was higher in Group I than II (11.9 ± 1.2, 11.3 ± 0.9, respectively, $P = 0.041$). The TBARS level was not statistically different between preterm and term deliveries. Nine out of 11 patients who developed hypertension during pregnancy had preeclampsia. The final TBARS level was significantly higher in these women ($P = 0.000$).

Conclusions: Daily supplementation with ferrous sulphate results in greater lipid peroxidation than weekly supplementation, the latter is comparable with daily iron (III)-hydroxide polymaltose complex. Lipid peroxidation levels are significantly higher in preeclampsia.

Key words: intermittent, iron, lipid peroxidation, polymaltose, pregnancy.

Introduction

Iron deficiency is the most common nutritional disorder in the world, especially in developing countries. During pregnancy, universal iron supplementation from the second trimester onwards is the standard recommendation because of the high prevalence of anemia, poor dietary intake and inability to meet the increased iron requirements of pregnancy. However, it is being recognized that current recommendations may be higher than necessary.[1] Higher iron doses have a high incidence of undesirable side-effects leading to poor compliance. Also, iron in excess is an active participant in the Fenton reaction, which results in the production of free radicals and lipid peroxidation.[2] Therefore, there are concerns that high doses of iron as

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a fortificant or as a dietary supplement may be associated with increased oxidative damage.[3] Lipid peroxidation has been found to be significantly increased in women receiving daily iron and vitamin C supplements compared to a control group of unsupplemented pregnant women.[4] Free iron can have a pro-oxidant effect catalyzing the generation of free radicals *in vivo* via the Fenton and Haber–Weiss reactions. Free radicals react with unsaturated fatty acids forming lipid peroxides, which cause membrane damage and cell injury. Damage from free radicals and lipid peroxidation has been implicated in the causation of pregnancy complications such as preeclampsia[5,6] and intrauterine growth restriction (IUGR).[7] Thus, excess iron can lead to possible adverse effects for both mother and fetus.

In several countries, a weekly approach to iron supplementation has been reported to be a safe, efficacious and cost-effective method to prevent anemia in pregnant women.[8–12] It is associated with fewer side-effects, better compliance and possibly a reduction in oxidative damage. So far, only animal studies have compared the effects of daily and intermittent oral iron supplementation on lipid peroxidation.[13] Recently, iron (III)-hydroxide polymaltose complex (IPC) has been introduced, whose bioavailability after oral administration is good with a lower rate of treatment interruption related to lesser upper gastrointestinal tract adverse events. The aim of this study was to compare the effects of daily versus weekly iron prophylaxis with iron sulphate on lipid peroxidation and hemoglobin levels in non-anemic pregnant women and to study their maternal and perinatal outcome, as well as to compare similar endpoints with daily IPC administration.

Material and Methods

This study was a randomized prospective trial conducted from April 2002 through April 2004 in the Departments of Obstetrics and Gynecology, Hematology and Pharmacology. Pregnant women between 14 and 18 weeks' gestation with no prior intake of iron supplements were invited to participate in the study. Exclusion criteria were: hemoglobin <11.0 g/dL, packed cell volume (PCV) <30; cigarette smoking; pre-existing hypertension or diabetes; history of chronic illness, e.g. liver or renal disease, tuberculosis, heart disease, malaria; history of bleeding disorders, bleeding piles, chronic peptic ulcer; thalassemia or other hemoglobinopathies; intake of drugs such as anti-epileptics, non-steroidal anti-inflammatory drugs (NSAIDs), antithyroid medication, vitamins, antioxidants; multiple pregnancy; and prior history of blood transfusion. Informed written consent was obtained.

Participants were randomly allocated into three different iron supplementation groups, using a computer generated random number table. Patient and doctor were both aware of the allotted groups. Groups I and II received the standard Government of India supply of Irofol (large) tablets (Nestor Pharmaceuticals Ltd., Faridabad, Haryana, India), marketed in blister packs of 10 tablets, throughout the study. Each red-colored (Ponceau 4R) film-coated tablet contained dried ferrous sulphate 335 g (Indian Pharmacopeia) equivalent to 100 mg of elemental ferrous iron and 500 micrograms folic acid (IFA). Women in group I were supplied with three blister packs (30 tablets) for one month and instructed to take one tablet daily. Women in group II were supplied with one blister pack (10 tablets) for a month and instructed to take two tablets on any one day of the week – one before lunch and the other before dinner (total 200 mg elemental iron/week). No tablets were taken during the rest of the week. Group III received IPC tablets daily containing Iron (III) Hydroxide Polymaltose equivalent to 100 mg elemental iron and folic acid 350 micrograms, namely Ferium tablets (Emcure Pharmaceuticals Ltd., Pune). All groups received health education regarding the importance of diet in pregnancy, iron-rich foods and appropriate dietary practices and were instructed to take the tablets 30 min before meals and not with tea, coffee or milk. They were also advised to take calcium supplements after meals.

Patients were informed about the usual side-effects of iron preparations and asked to report nausea, vomiting, bowel disturbances or other side-effects, and to report if severe intolerance caused them to stop taking supplements.

The first visit

A detailed history was obtained including dietary history and assessment of socioeconomic status, and physical examination was carried out. Routine antenatal investigations were carried out along with detailed hematological work-up. One milliliter of venous blood was collected in ethylenediamine tetra-acetic acid (EDTA) vials and a complete blood count was done including hemoglobin, platelets, hematocrit (HCT), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC) using an autoanalyzer (K 1500,

Sysmex, Singapore). A peripheral smear stained with Leishman's stain was made to type anemia and exclude thalassemia. Five milliliters of venous blood was collected, and the serum separated and stored at –70°C for estimation of serum thiobarbituric acid reactive substances (TBARS) and glutathione levels. The technician who performed the blood tests was not aware of the group to which the patient was allocated. Stool examination was carried out in all cases and deworming done, if required, with mebendazole 100 mg twice daily for 3 days in the second trimester.

Follow up

Patients were advised to bring back their blister packs at the next antenatal visit. Compliance was verified verbally and by checking the used blister packs. The complete hematological work-up was repeated at 30–34 weeks' gestation. All women were followed up to term. Any complications occurring during the antenatal or intranatal periods were recorded. The total number of tablets consumed until delivery, period of gestation at delivery, mode of delivery and birthweight were noted.

Estimation of serum lipid peroxides

Estimation of TBARS and glutathione was done as follows:

Estimation of TBARS

A 0.5-mL serum sample was reacted with 0.2 mL of 8.1% sodium dodecyl sulphate, 1.5 mL of 20% acetic acid (pH 3.5), and 1.5 mL of 0.81% thiobarbituric acid. The mixture was heated in boiling water for 1 h, then cooled to room temperature. Five mL of butanol pyridine (15:1 v/v) solution was added and centrifuged at 5000 r.p.m. for 15 min. The upper organic layer was separated and the resulting pink color read spectrofluorimetrically at 515 nm excitation and 535 nm emission wavelengths. Standard solution prepared from 1,1,3′,3′-tetramethoxy propane was used as reference to obtain a standard curve.

Estimation of glutathione

Frozen serum samples were brought to room temperature. Protein was precipitated with 5% trichloroacetic acid. After processing the supernatant, the contents were centrifuged at 5000 r.p.m. for 15 min. To 0.5 mL of supernatant obtained, 4 mL of 0.3 M Na_2HPO_4 and 0.5 mL of DTNB (0.6 mm) [5-5′-dithiobis(2-nitrobenzoic acid)] in 1% trisodium citrate were added in succession. The intensity of the resulting yellow color was read spectrophotometrically at 412 nm. Reduced glutathione was used as the standard.

Statistical analysis

Statistical analysis was done by ANOVA using the SPSS 10 statistical package.

Results

A total of 109 women were enrolled in the study. Nineteen women dropped out of the study, including two who were excluded because of miscarriage and intrauterine demise respectively (Fig. 1). Complete data were available for analysis in 90 women, 30 in each group. Reasons for attrition common to all groups included change of residence, refusal of second blood collection and loss to follow up. More women complained of severe gastrointestinal intolerance with IFA than with IPC, with four women in the daily IFA group and one in the weekly IFA group changing to another preparation.

Table 1 shows the baseline characteristics of the recruited and excluded subjects. There was no significant difference between the three groups in terms of age, body mass index (BMI) and parity. Overall 49% were vegetarian and 51% were non-vegetarian. Dietary patterns and socioeconomic status were similar between groups. Baseline hemoglobin, hematocrit, MCV and MCHC, TBARS and glutathione were comparable but baseline MCH was significantly higher in the IFA daily compared to IPC daily group ($P = 0.007$).

The mean gestation at which supplementation was started was 16.1 ± 1.3 weeks and mean duration of iron supplementation before final sampling was 17.9 ± 1.4 weeks. These were not significantly different between Group I (IFA daily) and Group III (IPC daily). However in Group II (IFA weekly), iron supplementation was started significantly earlier ($P = 0.005$) and subjects received supplementation for a significantly longer duration ($P = 0.002$) than Group I.

In the IFA daily group there was a highly significant ($P = 0.000$) increase in TBARS, and the final TBARS level was significantly higher than both IFA weekly and IPC daily groups (Table 2). In both the other groups the change in TBARS was not significant. There was a marginal fall in glutathione level in all three groups at the end of supplementation which was not statistically significant (Table 2).

Hematological values at the beginning and end of supplementation: Table 3 shows that in the IFA daily

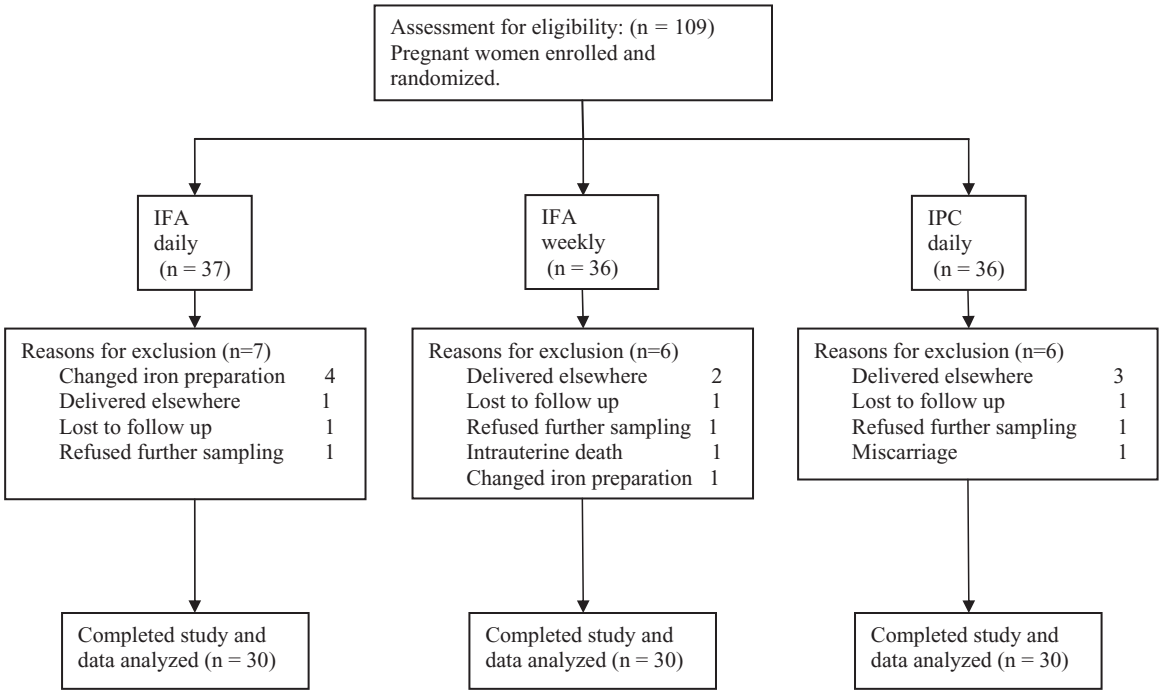

Figure 1 Assignment of pregnant women to weekly or daily supplementation regimens and reasons for dropout or exclusion. IFA, iron folic acid; IPC, iron (III)-hydroxide polymaltose complex.

Table 1 Characteristics of recruited and excluded subjects

Characteristics	Completed study ($n = 90$)	Excluded ($n = 19$)	P-value
Socio-demographic parameters			
Age (years)	25.6 ± 3.1	24.9 ± 2.4	0.325
Parity (n)	0.4 ± 0.7	0.3 ± 0.5	0.671
BMI (kg/m^2)	23.6 ± 1.5	24.1 ± 1.3	0.171
POG at start of supplementation (weeks)	16.1 ± 1.3	16.1 ± 1.3	0.984
Duration of follow up (weeks)	38.4 ± 1.2	25.6 ± 3.6	0.000*
Baseline parameters			
Hemoglobin (g/dL)	11.67 ± 0.71	11.56 ± 0.48	0.547
TBARS (μmol/L)	2.32 ± 0.15	2.36 ± 0.06	0.151
Glutathione (μmol/L)	7.04 ± 1.40	7.12 ± 1.46	0.835
Gastrointestinal side-effects	21.10%	26.30%	0.619

*Significant. Values are expressed as mean ± S.D. BMI, body mass index; POG, period of gestation; TBARS, thiobarbituric acid reactive substances.

group there was a marginal increase in hemoglobin at the end of supplementation while there was a marginal fall in both the IFA weekly and IPC daily groups. Only the marginal fall in hemoglobin in the IFA weekly group was significant ($P = 0.004$). The final hemoglobin value in the IFA daily group was significantly higher than that in the IFA weekly group ($P = 0.041$) despite the fact that the IFA weekly group subjects received supplementation for a significantly longer period than the IFA daily group. A fall in MCV was noted in all groups (Table 3).

Overall 22.2% of women were non-compliant: 12 (40%) women in the IFA daily group and four (13.3%) women each in the IFA weekly and IPC daily groups did not comply with the prescribed schedule ($P = 0.016$). Nineteen (21%) women complained of side-effects (Table 4), of whom 57.9% were non-compliant. The incidence of side-effects in the IFA daily group was significantly higher than in the other two groups ($P = 0.001$) and was the reason for the higher incidence of non-compliance, 75% being due to gastrointestinal side-effects.

Table 2 Lipid peroxidation and antioxidant status at the beginning and end of supplementation

Study group	Baseline	Final	Difference	*P*-value
IFA daily ($n = 30$)				
TBARS (μmol/L)	2.29 ± 0.15	2.90 ± 0.31**	0.61 ± 0.26	0.000*
Glutathione (μmol/L)	7.10 ± 1.49	7.10 ± 1.48	–0.003 ± 0.08	0.809
IFA weekly ($n = 30$)				
TBARS (μmol/L)	2.32 ± 0.14	2.34 ± 0.12	0.02 ± 0.06	0.096
Glutathione(μmol/L)	7.00 ± 1.36	6.98 ± 1.37	–0.02 ± 0.08	0.224
IPC daily ($n = 30$)				
TBARS (μmol/L)	2.33 ± 0.15	2.34 ± 0.13	0.007 ± 0.06	0.519
Glutathione (μmol/L)	7.03 ± 1.39	7.02 ± 1.41	–0.01 ± 0.11	0.600

*Significant. **Significantly different from corresponding values in IFA weekly and IPC daily groups ($P = 0.000$). IFA, iron folic acid; IPC, iron(III)-hydroxide polymaltose complex; TBARS, thiobarbituric acid-reactive substances.

Table 3 Hematological values at the beginning and end of supplementation

Study group	Baseline (mean ± S.D.)	Final (mean ± S.D.)	Difference (mean ± S.D.)	*P*-value
IFA daily ($n = 30$)				
– Hb	11.79 ± 0.84	11.86 ± 1.15*	0.08 ± 1.14	0.71
– HCT (%)	35.32 ± 1.42	35.40 ± 2.15	0.08 ± 2.17	0.82
– MCH (pg)	33.52 ± 1.21***	32.99 ± 2.15	–0.53 ± 2.37	0.20
– MCV (fl)	85.11 ± 2.18	84.09 ± 2.80	–1.02 ± 2.54**	0.04
– MCHC (g/dL)	34.13 ± 1.37	34.07 ± 2.28	–0.05 ± 2.18	0.89
IFA weekly ($n = 30$)				
– Hb	11.64 ± 0.62	11.25 ± 0.90	–0.39 ± 0.71	0.004
– HCT (%)	35.19 ± 1.20	34.24 ± 1.93	–0.96 ± 1.63	0.04
– MCH (pg)	32.97 ± 1.13	31.81 ± 2.16	–1.16 ± 1.76	0.001
– MCV (fl)	86.29 ± 1.91	83.08 ± 2.88	–3.21 ± 3.48	0.000
– MCHC (g/dL)	34.57 ± 0.94	33.63 ± 1.36	–0.94 ± 1.27	0.000
IPC daily ($n = 30$)				
– Hb	11.58 ± 0.65	11.55 ± 0.75	–0.04 ± 0.76	0.79
– HCT (%)	34.77 ± 1.36	34.66 ± 1.48	–0.11 ± 1.46	0.63
– MCH (pg)	32.57 ± 1.19	32.74 ± 1.52	0.17 ± 1.34	0.48
– MCV (fl)	86.16 ± 1.62	85.54 ± 1.55	–0.62 ± 1.99	0.09
– MCHC (g/dL)	34.37 ± 1.12	34.11 ± 1.27	–0.27 ± 1.46	0.33

*Significantly different from corresponding value in IFA weekly group ($P = 0.041$); **Significantly different from corresponding value in IFA weekly group ($P = 0.008$); ***Significantly different from corresponding value in IPC daily group ($P = 0.007$). Hb, hemoglobin; HCT, hematocrit; IFA iron folic acid; IPC, iron(III)-hydroxide polymaltose complex; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume.

The mean number of total tablets consumed until delivery was 141.5 ± 13.4 in the IFA daily group, 45.7 ± 3.0 in the IFA weekly group and 146.7 ± 18.9 in the IPC daily group, respectively. Women in the IFA weekly group consumed significantly fewer tablets than those in the other two groups ($P = 0.000$).

All 90 women were followed until delivery. Mean gestation at delivery was 38.3 ± 1.2 weeks in the IFA daily group, 38.2 ± 1.3 weeks in the IFA weekly group and 38.5 ± 1.2 weeks in the IPC daily group and was comparable. Overall 12% ($n = 11$) of women delivered preterm: three in the IFA daily group, five in the IFA weekly group and three in the IPC daily group. The mean TBARS level was not statistically different between women who delivered preterm and at term (2.43 ± 0.28 μmol/L and 2.54 ± 0.34 μmol/L, respectively).

There was no significant difference in the incidence of pregnancy complications between the three groups. Eleven patients had hypertension during pregnancy, nine of whom had preeclampsia: four in the IFA daily group, three in the IFA weekly group and two in the

Table 4 Side-effects

Side-effects	IFA daily ($n = 30$)	IFA weekly ($n = 30$)	IPC daily ($n = 30$)	Total ($n = 90$)
Nausea/vomiting	5	2	2	9
Diarrhea	3	0	0	3
Constipation	1	0	0	1
Metallic taste	2	0	1	3
Epigastric discomfort	2	1	0	3
Total	13 (43.3%)	3 (10%)	3 (10%)	19 (21%)

IFA iron folic acid; IPC, iron(III)-hydroxide polymaltose complex.

IPC daily group. The final TBARS level was significantly higher in women who developed preeclampsia ($n = 9$) in comparison to normotensive women ($n = 79$): 2.98 ± 0.62 μmol/L versus 2.48 ± 0.25 μmol/L, P = 0.000.

The mode of delivery was not significantly different between the three treatment groups. Cesarean section was done in 24 (26.7%) women. Mean birthweight was 2.64 ± 0.34 kg in the IFA daily group, 2.69 ± 0.36 kg in the IFA weekly group and 2.65 ± 0.37 kg in the IPC daily group. Low birthweight (LBW) <2.5 kg was seen in 22 (24.4%) babies: seven in the IFA daily group, eight in the IFA weekly group and seven in the IPC daily group. Eight of these were preterm and five were appropriate for gestational age. Of 14 LBW babies born at >37 weeks, two had associated pregnancy-induced hypertension (PIH) and one had associated oligohydramnios. Low birthweight was not found to be related to the maternal final hemoglobin or lipid peroxidation status. The maternal final TBARS level where the birthweight was <2.5 kg and ≥2.5 kg was 2.51 ± 0.25 μmol/L and 2.54 ± 0.36 μmol/L, respectively (P = NS). There was no significant difference in placental weight, 1 min Apgar score or incidence of meconium in the three groups.

Discussion

The impact of intermittent iron supplementation and its efficacy in the community has been evaluated in several countries including Bangladesh, Indonesia, China, Northern Malawi and India.[1,8–10,12] These studies reported intermittent supplementation on a weekly or biweekly basis to be safe, efficacious and cost-effective.

As in the present study, most of these studies did not include a placebo group due to ethical reasons, as there is evidence that all women in developing countries do require prophylactic iron. Only non-anemic pregnant women were included because iron deficiency *per se* can increase lipid peroxidation[13] and also because our previous experience suggested that intermittent iron supplementation may not be sufficient to sustain hemoglobin levels in anemic pregnant women.[12]

The TBARS level and the TBARS/vitamin E ratio has been shown to be significantly higher in women who received a daily combined supplement of 100 mg ferrous fumarate and 500 mg of vitamin C in the last trimester of pregnancy[4]. We found that daily administration of IFA resulted in a highly significant increase in TBARS ($P = 0.000$) unlike weekly IFA and daily IPC intake. IPC contains iron in the ferric form combined with polymaltose, which causes less oxidative stress than ferrous salts. Ferrous sulphate increases the susceptibility of atherogenic lipoproteins LDL and VLDL to oxidation while IPC intake results in a significant decrease in conjugated dienes – a lipid peroxidation product.[14]

Glutathione, a physiological antioxidant, scavenges free radicals and reactive oxygen species (e.g. hydroxyl radical, lipid peroxyl radical, H_2O_2) directly or indirectly through enzymatic reactions. Its levels are expected to decline whenever there is increased production of lipid peroxides. The decrease in glutathione concentration in all three groups is indicative of increase in oxidative stress above that in normal pregnancy.

Free radicals and lipid peroxidation have been implicated in ageing and various diseases in humans including cancer, multiple sclerosis, Parkinson's disease, rheumatoid arthritis and atherogenesis, eventually leading to coronary artery disease and stroke.[15–17] In pregnancy, lipid peroxidation causes imbalance between the production of prostacyclin and thromboxane A2 which has been implicated in the pathogenesis of preeclampsia.[18] Uncontrolled lipid peroxidation overwhelms the protective mechanisms of antioxidants causing vascular endothelial dysfunction that can lead to preeclampsia.[19] A positive correlation between levels of lipid peroxidation products and severity of preeclampsia has been reported,[20,21]

however there are some reports that lipid peroxidation is not increased in preeclampsia.[22,23] In the present study, the mean TBARS level at 30–34 weeks in the preeclamptic patients was significantly higher than in normotensive counterparts. Although antioxidant was not added to the serum samples prior to analysis, the samples were immediately stored at –20°C. At such low temperatures all intracellular metabolic and biochemical processes are suppressed. Thus, the increased levels of TBARS in preeclamptic women reflect increased lipid peroxidation *in vivo*.

Karowicz found higher levels of oxidative stress indices of cell membrane damage like malondialdehyde (MDA), Schiff bases, lipid peroxides and conjugated dienes in IUGR than in normal pregnancy.[7] The concentration of 8-isoprostane was higher in women with IUGR than in normal pregnant women.[24] We did not find any difference in the maternal final TBARS level among LBW and IUGR cases, however the number of these cases was small.

The mean hemoglobin level showed a comparable treatment effect between the three groups. The slight decrease in the mean hemoglobin value in the IFA weekly group was not clinically significant as it remained >11 g/dL in 70% of women in this group. Our previous study also showed that in non-anemic women there was no significant change in hemoglobin levels with either daily or weekly supplementation.[12] Previous studies that have shown a significant increase in hemoglobin level with iron supplementation[1,8,10] were field studies that dealt predominantly with anemic women.

IPC has been shown to have good efficacy for treatment of iron deficiency anemia in pregnancy,[25,26] although isolated case reports have reported its ineffectiveness.[27,28] We found the efficacy of IPC was comparable to that of ferrous sulphate with the additional benefit of reduction in oxidative stress, particularly in the context of long-term supplementation.

In the present study, the lesser incidence of gastrointestinal side-effects in the IFA weekly group improved compliance in the former. Among women taking IFA (daily or weekly) with side-effects, only 31.3% had taken all tablets, whereas 88.6% of women with no complaints had consumed all tablets. Likewise, Ridwan reported that only 20.8% of those with complaints had taken all tablets compared to 63.5% of women with no complaints.[8] Hyder reported that vomiting occurred more frequently in the weekly (21%) than in the daily group (11%, $P < 0.05$), perhaps because of the higher dose on that day. In spite of this, compliance was higher compared to the daily group (93% vs 61%, respectively, $P < 0.05$).[29] In contrast, side-effects in the IPC daily group were mild and did not affect compliance. Similar results have been reported in other studies comparing IPC with ferrous fumarate and ferrous sulphate.[27,30] A probable explanation for the poorer tolerability and greater increase in lipid peroxidation with ferrous sulphate compared to IPC is the difference in mucosal uptake and pharmacokinetics of the two preparations.[31] Ferrous sulphate is absorbed rapidly by passive uncontrolled diffusion by the gastrointestinal mucosal cells. Ferrous iron has a low molecular weight and continues to enter the circulation by passive diffusion across the mucosal cell even if transport mechanisms are saturated causing iron overload. IPC is absorbed and exchanged to transport proteins very slowly and in a controlled manner due to polynuclear structure, thus avoiding rapid increase in serum iron. Thus IPC can be effectively given in pregnant women without the risk of side-effects.

Maternal and perinatal outcomes were comparable in the three groups with respect to the complications during pregnancy, period of gestation at delivery, mode of delivery, indication for cesarean section, birthweight, placental weight, incidence of meconium and neonatal Apgar score. This was similar to our previous experience comparing the effect of daily and intermittent iron supplementation on pregnancy outcome.[12] Gomber *et al*. (2002) found that birthweight and placental weight increased significantly with the rise in maternal hemoglobin levels.[11] In the present study, however, there was no association between birthweight and maternal hemoglobin level, probably because only non-anemic women were included. Lipid peroxidation was found to be significantly higher in all women who developed preeclampsia. There was no difference in the incidence of preeclampsia between the three groups, but the sample size of this sub-group was small.

In conclusion, daily supplementation with ferrous sulphate leads to a significant increase in lipid peroxidation compared to weekly supplementation. Weekly supplementation has no adverse effect on hemoglobin in non-anemic pregnant women and is better tolerated with fewer side-effects. IPC is as efficacious as ferrous sulphate in maintaining hemoglobin levels in non-anemic pregnant women and is also well tolerated. Lipid peroxidation levels as well as side-effects with daily IPC are comparable with weekly ferrous sulphate.

References

1. Ekström EC, Hyder SM, Chowdhury AM *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.
2. Gutteridge JM. Iron and free radicals. In: Hallberg L, Asp NG (eds). *Iron Nutrition in Health and Disease*. London: John Libbey and Co, 1996; 239–246.
3. Beard JL. Effectiveness and strategies of iron supplementation during pregnancy. *Am J Clin Nutr* 2000; **71** (5 Suppl): 1288S–94S.
4. Lachili B, Hininger I, Faure H *et al.* Increased lipid peroxidation in pregnant women after iron and vitamin C supplementation. *Biol Trace Elem Res* 2001; **83**: 103–110.
5. Wang YP, Walsh SW, Guo JD, Zhang JY. Maternal levels of prostacyclin, thromboxane, vitamin E and lipid peroxides throughout normal pregnancy. *Am J Obstet Gynecol* 1991; **165**: 1690–1694.
6. Cargnoni A, Gregorini G, Ceconi C, Majorca R, Ferrari R. Lipid peroxidation in normal pregnancy and preeclampsia. *Adv Exp Med Biol* 1994; **366**: 420–421.
7. Karowicz-Bilinska A, Suzin J, Sieroszewski P. Evaluation of oxidative stress indices in treatment of pregnant women with IUGR. *Med Sci Monit* 2002; **8**: CR211–CR216.
8. 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**: 884–890.
9. 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**: 341–347.
10. 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**: 84–88.
11. Gomber S, Agarwal KN, Mahajan C, Agarwal N. Impact of daily versus weekly hematinic supplementation on anemia in pregnant women. *Indian Paediatr* 2002; **39**: 339–346.
12. 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**: 409–417.
13. Knutson MD, Walter PB, Ames BN, Viteri FE. Both iron deficiency and daily iron supplements increase lipid peroxidation in rats. *J Nutr* 2000; **130**: 621–628.
14. Tuomainen TP, Nyyssönen K, Salonen R, Baumgartner JA, Geisser P. Oral supplementation with ferrous sulfate but not with non-ionic iron polymaltose complex increases the susceptibility of plasma lipoproteins to oxidation. *Nutr Res* 1999; **19**: 1121–1132.
15. Halliwell B, Gutteridge JM. Lipid peroxidation, oxygen radicals, cell damage and antioxidant therapy. *Lancet* 1984; **1**: 1396–1397.
16. Hall ED, Braughler JM. Central nervous system trauma and stroke. II. Physiological and pharmacological evidence for involvement of oxygen radicals and lipid peroxidation. *Free Radic Biol Med* 1989; **6**: 303–313.
17. Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum JL. Beyond cholesterol. Modifications of low-density lipoprotein that increase its atherogenicity. *N Engl J Med* 1989; **320**: 915–924.
18. Szczeklik A, Gryglewski RJ, Domagula B, Dworski R, Basista M. Dietary supplementation with vitamin E in hyperlipoproteinemias: Effects on plasma lipid peroxides, antioxidant activity, prostacyclin generation and platelet aggregability. *Thromb Haemost* 1985; **54**: 425–430.
19. Hubel CA, Roberts JM, Taylor RN, Musci TJ, Rogers GM, McLaughlin MK. Lipid peroxidation in pregnancy: new perspectives on preeclampsia. *Am J Obstet Gynecol* 1989; **161**: 1025–1034.
20. Madazli R, Benian A, Gümüstas K, Uzun H, Ocak V, Aksu F. Lipid peroxidation and antioxidants in preeclampsia. *Eur J Obstet Gynecol Reprod Biol* 1999; **8**: 205–208.
21. Serdar Z, Gür E, Colakoethullarý M, Dewelioethlu O, Sarandöl E. Lipid and protein oxidation and antioxidant function in women with mild and severe preeclampsia. *Arch Gynecol Obstet* 2003; **268**: 19–25.
22. Morris JM, Gopaul NK, Endresen MJ *et al.* Circulating markers of oxidative stress are raised in normal pregnancy and pre-eclampsia. *Br J Obstet Gynaecol* 1998; **105**: 1195–1199.
23. Regan CL, Levine RJ, Baird DD *et al.* No evidence for lipid peroxidation in severe preeclampsia. *Am J Obstet Gynecol* 2001; **185**: 572–578.
24. Karowicz-Bilinska A, Kowalska-Koprek U, Suzin J, Sieroszewski P. [Analysis of 8- isoprostane concentration as a marker of oxidative stress in pregnant women diagnosed with IUGR]. *Ginekol Pol* 2003; **74**: 1137–1142. (In Polish.)
25. Reddy PS, Adsul BB, Gundewar K, Desai A. Mumfer (iron polymaltose complex) in the management of anaemia in pregnancy: An Indian study. *J Indian Med Assoc* 2000; **98**: 343–346.
26. Walawalkar SS, Chugh S. A randomized, controlled trial of ferric hydroxide polymaltose complex and ferrous fumarate in anaemia in pregnancy. *JAMA India – The Physicians Update* 2001; **4**: 36–40.
27. Mehta BC. Iron hydroxide polymaltose: Iatrogenic cause of persistent iron deficiency anaemia despite continuous oral iron therapy. *J Assoc Physicians India* 2002; **50**: 279–280.
28. Bichile SK, Kumar V. Persistent iron deficiency anaemia. *J Assoc Physicians India* 2002; **50**: 617–618.
29. Hyder SM, Persson LA, Chowdhury AM, Ekström 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**: 175–179.
30. Jacobs P, Wood L, Bird AR. Erythrocytes: Better tolerance of iron polymaltose complex compared with ferrous sulphate in the treatment of anaemia. *Hematology* 2000; **5**: 77–83.
31. Johnson G, Jacobs P. Bioavailability and the mechanisms of intestinal absorption of iron from ferrous ascorbate and ferric polymaltose in experimental animals. *Exp Hematol* 1990; **18**: 1064–1069.