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# Comparative study of daily Vs intermittent iron supplementation in pregnant women

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**Abstract**
**Background:** Pregnancy is a time in which the risk for developing iron deficiency anemia is highest, because iron requirements are substantially greater than average absorbable iron intakes. This aim of this study to evaluate the whether weekly antenatal oral iron and folate supplementation is an effective alternative to a daily regimen in non-anemic pregnant women to prevent anemia and iron deficiency during the third trimester.
**Material & Methods:** Women having periods of gestation (POG) between 14 to 16 weeks, who were recruited for the study. Informed written consent was obtained from all women, and ethical approval for the study was obtained from the SMS, Jaipur. The hematocrit, hemoglobin and serum ferritin level was assessed. All women were first given single dose of tab albendazole 400 mg. Then they were randomly allocated to the three treatment groups and given a haematinic capsule i.e. 200mg of ferrous sulfate (60mg elemental iron) with 1mg folic acid tablet either weekly (n=26), thrice weekly (n=35) or daily (n=31).
**Results:** The compliance was good in all three study groups and no serious side-effects were reported. There were no significant differences in income, educational level, age, parity, POG, initial Hb and SF concentrations, Hct, and duration of previous haematinic prophylaxis between the three study groups. There is a reduction in the number of women with IDA in all three supplementation groups, but the number of women with ID is significantly increased in the weekly supplementation group and significantly decreased in the daily supplementation group.
**Conclusion:** Prophylactic oral iron supplements when given intermittently were not effective in preventing iron deficiency anaemia in pregnancy. In non-anemic pregnant women, a weekly regimen is an effective alternative to a daily regimen for antenatal oral iron and folate supplementation for preventing anemia and iron deficiency during the third trimester.

**Keywords:** Iron supplementation, pregnancy, serum ferritin, hemoglobin, hematocrit

## Introduction
Iron deficiency continues to be the leading single-nutrient deficiency in the world, affecting the lives of > 2 billion persons despite considerable efforts to decrease its prevalence for the past 3 decades [1, 2]. Primary focuses have been to increase the amount and bioavailability of iron in the diet [3-5], to control infections that contribute to iron losses from the body [6], and to improve economic, educational, and social conditions that contribute to the high prevalence of iron deficiency [7, 8].
Nutritional iron deficiency is highest in population segments that are at peak rates of growth, namely, infants, young children, and pregnant women. Pregnancy is a time in which the risk for developing iron deficiency anemia is highest, because iron requirements are substantially greater than average absorbable iron intakes.
The overall iron requirement during pregnancy is significantly greater than that in the nonpregnant state despite the temporary respite from iron losses incurred during menstruation. Iron requirements increase notably during the second half of pregnancy because of the expansion of the red blood cell mass and the transfer of increasing amounts of iron to both the growing fetus and the placental structures. Iron is also lost in maternal blood and lochia at parturition. The degree to which these increased requirements can be met depends on the size of iron stores at the start of pregnancy and on the amounts of dietary iron that can be absorbed during pregnancy. The fact that iron deficiency anemia frequently develops in pregnancy indicates that the physiologic adaptations are often insufficient to meet the increased requirements. As a result, iron supplementation during pregnancy is a common practice throughout the world.

In recent years, oral iron supplementation program has been focused from daily doses to intermittent doses (once or twice weekly). Many studies have been conducted in various parts of world and most of the studies showed that the increase in hemoglobin level were similar to daily supplementation. The hypothesis behind intermittent iron supplementation has been based on "mucosal block" theory of iron absorption [9]. The gut has a mechanism to prevent entry of excess iron in the body. The mucosal cells absorb iron on the basis of iron requirement of the body. The iron reaching inside the mucosal cell is either transported to plasma or oxidized to ferric form and complexed with apoferritin to form ferritin. This ferritin generally remains stored in the mucosal cells and is lost when they are shed (gut mucosal turnover rate 3-4 days). This is called the ferritin curtain [10]. The iron status of body and erythropoietic activity govern the balance between these two processes. Though iron requirement during the first trimester is reduced but in the second and third trimesters it rises to between 4 and 6 mg, respectively [11].

Physiologic demands for iron increase from 0.8 to ≤7.5 mg absorbed Fe/d, although there is considerable debate about the exact upper limits of this increased iron demand in the third trimester of pregnancy [12, 13]. Such demands result in a decline in iron stores during pregnancy and ultimately can produce iron-deficient erythropoiesis and anemia because a positive or even neutral iron balance is difficult to attain. The median need for iron in the second and third trimesters of pregnancy is calculated to be nearly 4.6 mg Fe/d, whereas the 90th percentile is 6.7 mg Fe/d.[12] These calculations are based on the estimation that the median iron need during pregnancy is 840 mg, with a 90th percentile of 1210 mg. If the iron needs for 6 mo of lactation are considered, the median total iron requirement would be 1018 mg absorbed Fe. This calculation translates into an additional median need of 426 mg Fe for this 15-mo period.

Strong evidence shows that iron deficiency in the first trimester of pregnancy results in significant decrements in fetal growth, whereas iron deficiency anemia in the second and third trimesters has little effect on fetal growth [14, 15]. Most perinatal iron intervention programs rely on the initiation of treatment at the first visit of the newly pregnant woman to her health care provider, somewhere around 10–15 wk of pregnancy. It is possible, however, that by this time the real window of opportunity for a positive intervention against iron deficiency has passed if fetal growth and development are the dependent variables considered. This aim of this study to evaluated whether weekly antenatal oral iron and folate supplementation is an effective alternative to a daily regimen in non-anemic pregnant women to prevent anemia and iron deficiency during the third trimester.

## Material & Methods

Women having periods of gestation (POG) between 14 to 16 weeks, who were recruited for the study. Informed written consent was obtained from all women. During venepuncture for other routine antenatal investigations an additional 2 ml of mixed venous blood was taken. The haematocrit (Hct) was estimated using haematocrit tubes, the haemoglobin (Hb) was estimated by the cyanmethaemolgobin method and serum ferritin (SF) by an immuno-radiometric assay technique using IRMA Ferritin Kits (Diagnostic Products Corporation, Los Angeles).

All women were first given single dose of tab albendazole 400 mg. Then they were randomly allocated to the three treatment groups and given a haematinic capsule i.e. 200mg of ferrous sulfate (60mg elemental iron) with 1mg folic acid tablet either weekly (n=26), thrice weekly (n=35) or daily (n=31). The women were advised to take the supplement with water at 11.00 a.m (approximately one hour before lunch).

Each woman was given either 6 (weekly group), 18 (thrice weekly group) or 42 (daily group) capsules at a time. The number of capsules remaining was checked at each visit. A second sample of mixed venous blood was obtained for Hb, SF and Hct estimations at 34 weeks of gestation. Hence the duration of supplementation varied from 20 weeks (in the women who had a gestation of 14 weeks at recruitment) to 18 weeks (in women who had a gestation of 16weeks at recruitment).

## Results

There were no significant differences in income, educational level, age, parity, POG, initial Hb and SF concentrations, Hct, and duration of previous haematinic prophylaxis between the three study groups (Table 1). Of the 92 women all had received primary education, and 22 (24%) tertiary education. Of 52 subjects who disclosed their income level 26 (50%) had a monthly family income of less than Rs. 3000. The compliance was good in all three study groups and no serious side-effects were reported.

**Table 1:** Analysis of variance

| Characteristics | Mean±SD | P-value |
|---|---|---|
| Age (yrs) | 25.1±5.6 | 0.7 |
| Parity | 1.8±0.9 | 0.2 |
| Gestation (weekly) | 18.8±3 | 0.9 |
| Pre prophylaxis (weeks) | 3.3±2.3 | 0.8 |
| Duration (weeks) | 15.2±2.4 | 0.06 |
| Pretreatment Hb (g/l) | 8.1±18 | 0.6 |
| Pretreatment Hct (%) | 35.7±2.9 | 0.2 |
| Pretreatment SF (microg/l) | 19.1±13.5 | 0.1 |

The results of supplementation are shown in Table 2 &3. There is a reduction in the number of women with IDA in all three supplementation groups, but the number of women with ID is significantly increased in the weekly supplementation group and significantly decreased in the daily supplementation group.

**Table 2:** Results of supplementation. Whole numbers indicate numbers of women in each group (*SF<12microg/l)*

| Supplementation | Pretreatment | Post treatment | P-value |
|---|---|---|---|
| Once a week (N=26) | 8 | 18 | <0.0001 |
| Thrice a week (N=35) | 12 | 23 | NS |
| Daily (N=31) | 10 | 21 | <0.0001 |
| Total (N=92) | 30 | 62 | |

**Table 3:** Results of supplementation. Whole numbers indicate numbers of women in each group (*Hb<11.0g/l)*

| Supplementation | Pretreatment | Post treatment | P-value |
|---|---|---|---|
| Once a week (N=26) | 24 | 2 | <0.0001 |
| Thrice a week (N=35) | 22 | 13 | NS |
| Daily (N=31) | 26 | 5 | <0.0001 |
| Total (N=92) | 72 | 20 | |

## Discussion

Contrary to our expectations only daily iron supplementation was effective in preventing iron deficiency. Although the sample size was small, highly significant increased risks of the subjects developing ID with the weekly and thrice weekly regimens were clearly seen. A significantly higher risk of developing IDA was seen in the weekly supplementation group. The possible higher

risk of IDA in the thrice weekly supplementation group may have reached statistical significance with a larger sample. The risk of developing IDA or ID did not appear to be influenced by either the initial Hb and SF (before supplementation) or the duration of supplementation. These findings too may be a result of the small sample size.

Though in our study the haemoglobin rise was more significant in daily group, it increased to a significant level in weekly group too and was maintained to a safe level. In study by Mumtaz *et al*. [16] too, the hemoglobin rose to a significant level in weekly group (p=0.0037).

Serum ferritin value which is a sensitive indicator of iron storage did not increase to a significant level (p=0.0661) in weekly group but in daily group the increase was significant ($p$<0.0001). Similar results were found in the study by Mumtaz *et al*. [16] where the serum ferritin level increased to a significant level in daily group ($p$<0.0001) whereas in weekly group it did not change (p=0.16). In the study by Sunil Gomber *et al*. [17] the ferritin values continued to be remain low during pregnancy irrespective of supplementation (p=0.63 within groups and p=0.40 between groups). In the study by A. Mukhopadhyay *et al*. [18] the baseline S. ferritin values were significantly different in both groups (p=0.027) with a lower value in weekly groups. There was no significant increase in S. ferritin values in both daily (p=0.477) and weekly group (p=0.680). Intergroup p values was 0.10. In study by Ridwan *et al*. [19], there were no significant within group changes in serum ferritin concentrations. But a small decrease in the weekly group together with a small increase in the daily group, however caused a small but significant difference between groups in treatment effect (p=0.049). In study by SMZ Hyder *et al*. [20] the baseline S. ferritin values were higher in weekly group (p=0.06).

A recent meta-analysis of eight studies could not find any evidence to justify changing the existing daily antenatal oral iron supplementation program to a weekly supplementation regimen [21]. Although there is a slight increase in the absorption of oral iron when the supplements are administered weekly this increase did not result in sufficient amounts being absorbed to meet the increased demand during pregnancy, especially in ID subjects [22]. Furthermore, there is no evidence to suggest that a weekly regimen would lead to improved compliance as most healthy subjects are poorly motivated to take prophylactic treatment [23].

According to the evidence available at present daily oral iron supplementation is recommended for pregnant women in communities at risk of IDA. Intermittent iron supplementation appears to be inappropriate.

## Conclusion

Prophylactic oral iron supplements when given intermittently were not effective in preventing iron deficiency anaemia in pregnancy. In non-anemic pregnant women, a weekly regimen is an effective alternative to a daily regimen for antenatal oral iron and folate supplementation for preventing anemia and iron deficiency during the third trimester.

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