Intermittent oral iron supplementation during pregnancy

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(Index words: Anaemia, iron deficiency, serum ferritin)

Abstract

Rationale It has been suggested that in pregnant women weekly iron supplements are as effective as daily supplements in preventing iron deficiency anaemia (IDA).

Objective To compare the effectiveness of prophylactic antenatal oral iron supplements given weekly, thrice weekly and daily in preventing IDA in pregnancy.

Design A randomised control trial.

Setting University antenatal clinic, (UANC) Galle.

Subjects and method An oral iron supplement containing 100 mg of elemental iron was randomly given weekly (n=26) thrice weekly (n=35) and daily (n=31) to 92 women who were 14 to 24 weeks pregnant. Haemoglobin (Hb), serum ferritin (SF) and haematocrit (Hct) were assessed before and after 12 to 20 weeks of supplementation and a logistic regression analysis carried out.

Results The risk of developing anaemia was significantly higher in the weekly (odds ratio 15, 95% CI 1.4-165.6, $p<0.03$) and possibly higher in the thrice weekly (odds ratio 3,95% CI 0.3-30.3. $p=0.3$) groups. The risk of developing iron deficiency (SF<12(ig/l) was also significantly higher in the weekly (odds ratio 18,95% CI 2.8-115.5, $p<0.003$) and thrice weekly (odds ratio 10, 95% CI 1.6-64.8, $p<0.02$) groups.

Conclusion Prophylactic oral iron supplements when given intermittently were not effective in preventing iron deficiency anaemia in pregnancy.

Introduction

A preliminary oral iron supplement has been shown to suppress intestinal absorption of subsequent oral iron doses for 2 to 3 days (1,2). Hence a daily supplementation regimen results in progressive blockage of further iron absorption. This is probably due to a suppression of mucosal uptake which lasts the mucosal cell turnover time and occurs even in the presence of iron deficiency (ID) (3,4). The troublesome gastrointestinal side-effects of daily oral supplements which are probably due to this temporary overloading of the intestinal mucosa with unabsorbed iron may be dose related (5). Hence intermittent supplementation has been recommended as an alternative (6,7,8,9,10).

. Several studies have shown that weekly iron supplements were as effective as daily supplements in preventing iron deficiency anaemia (IDA) in children, adolescents and non-pregnant women (11,12,13,14). Studies done in Indonesia (9) and Bangaladesh (10) have shown that antenatal oral iron supplements given weekly were equally effective as daily supplements in improving IDA even in pregnancy.

Preliminary trials conducted at the university antenatal clinic (UANC) Galle suggested that thrice weekly oral iron supplements were probably adequate to prevent IDA of pregnancy (15) and weekly supplements were probably inadequate, especialy in those with borderline ID (16). Hence a randomised controlled trial was done to compare the effectiveness of weekly, thrice weekly and daily oral iron supplementation in the prevention of IDA of pregnancy.

Methods

Women having periods of gestation (POG) between 14 and 24 weeks, who presented to the UANC Galle (n=92) were recruited for the study. Informed written consent was obtained from all women, and ethical approval for the study was obtained from the Faculty of Medicine, Galle.

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). This assay has a sensitivity of detecting 0.1 fig of SF/I.

All women were first given mebendazole 100 mg twice daily for 3 days. Then they were randomly allocated to the three treatment groups and given a haematinic capsule either weekly (n=26), thrice weekly (n=35) or daily (n=31). The objective of the study was to compare the effectiveness of intermittent with daily supplementation in preventing IDA and ID in clinical practice and not to evaluate the effects of the different regimens. Hence the haematinic used in the study was a preparationn which is freely available, relatively cheap and commonly used by pregnant women in Sri Lanka. It contained 100 mg of elemental iron (as ferrous fumarate 300 mg), vitamin B_{12} 10 pig, folic acid 5 mg, vitamin C 100 mg, vitamin B, 10 mg, vitamin B_6 10 mg and niacinamide 50 mg. The women were advised to take the supplement with water at 11.00 a.m (approximately one hour before lunch).

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The Hb is also affected by folate and vitamin B_{12} deficiencies. Most of the haematinics commonly used by pregnant mothers in the country have multivitamins in addition to the iron and folate as in the preparation used in the study. However, as the only known cause for a low SF level is iron deficiency (17,18,19,20) the presence of multivitamins will not affect ID and the results of this study.

The subjects were reviewed at 4-weekly intervals and a structured interview was used to obtain information regarding compliance and side-effects. 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 to 36 weeks of gestation. Hence the duration of supplementation varied from 12 weeks (in the women who had a gestation of 24 weeks at recruitment) to 20 weeks (in the women who had a gestation of 14 weeks at recruitment). The objective was to assess the effectiveness of the supplementation regimens before the onset of labour, In a study done earlier in the plantation sector of Sri Lanka, a longer duration of supplementation (>17 weeks) was found to be more effective in preventing IDA (21).

Analysis of variance was used to asses differences in age, parity gestation period educational level, income, initial Hb and SF concentrations, Hct and duration of any previous haematinic prophylaxis between the three study groups.

IDA in the third trimester was defined as a Hb less than 110 g/l and ID as SF less than 12 **ng**/1. A multivariate logistic regression analysis was done and the odds ratios calculated to compare the risks of developing IDA and ID between the three study groups.

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.

The results of supplementation are shown in Table 2. 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.

A multivariate logistic regression showed that the risk of developing IDA was significantly higher in the weekly (odds ratio 15,95% CI 1.4-165.6, p<0.03) and possibly higher in the thrice weekly (odds ratio 3, 95% CI 0.3-30.3, p=0.3) supplementation groups (Table 3).

There was a highly significant increased risk of developing ID in the weekly (odds ratio 18,95% CI 2.8-115.5, p=0.003) and the thrice weekly (odds ratio 10,95% CI 1.6-64.8, p<0.02) supplementation groups (Table 4).

Table 1. Analysis of variance

					ANOVA	
		x	s.d	95% a	F	p
Age	(years)	25.1	5.6	23.9-26.3	0.79	0.7
Parity		1.8	0.9	1.6-2.0	1.77	0.2
Gestation	(weeks)	18.8	3	18.1 -19.4	0.46	0.9
Income level					2.47	0.07
Educational level					0.77	0.5
Prev prophy	(weeks)	3.3	2.3	2.5-4.0	0.54	0.8
Duration	(weeks)	15.2	2.4	14.6-15.6	2.0	0.06
PreHb	(g/l)	81	18	78-85	0.92	0.6
Pre Hct	(%)	35.7	2.9	35.1-36.3	1.28	0.2
PreSF	(Hg/1)	19.1	13.5	16.4-22.0	1.41	0.1

(s.d = standard deviation; x= arithmetic mean; 95% CI confidence interval; prev prophy = women who have received iron supplements before being recruited for the study; Duration = duration of supplementation; Pre Hb = Hb before supplementation; Pre SF = SF before supplementation; Pre Hct = Hct before supplementation).

Table 2. Results of supplementation. Whole numbers indicate numbers of women in each group

		SF<12fig/l			*Hb<110g/l*		
Supplementation		*Pre*	*Post*	*P*	*Pre*	*Post*	*P*
Once a week	(n=26)	6	19	<0.001	26	10	<0.001
Thrice a week	(n=35)	7	18	NS	34	6	<0.001
Daily	(n=31)	7	4	<0.001	28	2	<0.001
Total	(n=92)	30	41		88	18	

(Pre = before supplementation; Post = after supplementation).

Table 3. Risk of developing IDA (Hb < 100 g/1)

Supplementation		*Odds ratio*	*95% CI*	*P*
Once a week	(n=26)	15	14-165.6	0.027
Thrice a week	(n=35)	3.1	0.3 - 30.3	0.333
Daily	(n=31)	0.9	0.5-17.7	0.966

Table 4. Risk of developing ID (SF < 112 ug/1)

Supplementation		*Odds ratio*	*95% CI*	
Once a week	(n=26)	18.1	2.8-115.5	0.002
Thrice a week	(n=35)	10.1	1.6-64.8	0.015
Daily	(n=31)	1	0.1-9.5	0.96

Discussion

Contrary to our expectations only daily iron supplementation was effective in preventing ID. 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.

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 supplemetation regimen (22). 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 (23). 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 (24).

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.

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Disease genes?

Genes are about health. It is foolish to talk of cancer genes, or disease genes, or even thalassaemia genes. Most genes are healthy genes. They code for proteins and functions that allow us to survive, and usually flourish. Their rich diversity ensures both our endless and wondrous variety as people, and our evolutionary survival. The human genome project helps us to know the power of the genome for humankind, for all our people, for now and the future. Appropriate data will allow us to harness that power better. (Bob Williamson. Our human genome - how can it serve us well? *Bulletin of the World Health Organization* 2001; **79:**1005)