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7?  
serum ferritin increased in daily dose  
No difference in hemoglobin in daily vs weekly.

Iron Sup

# Effects of weekly iron supplementation of pregnant Indonesian women are similar to those of daily supplementation<sup>1-3</sup>

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**ABSTRACT** The effect of daily rather than weekly iron supplementation was compared in women who were 8-24 wk pregnant. One group (n = 68) received 60 mg Fe/d, the second group (n = 71) received 120 mg Fe/wk, given at once. Supplementation of 11.3 wk on average, depending on gestational date at entry, was not supervised. Hemoglobin increased in both groups (P < 0.001), serum ferritin did not change significantly. There was no significant difference between groups for changes in hemoglobin and serum ferritin. In a subgroup of women with a hemoglobin concentration < 110 g/L at baseline (n = 45 daily; n = 54 weekly) no significant within-group changes occurred in serum ferritin, but the change in the daily group was 4.1 µg/L higher than in the weekly group (P = 0.049). Compliance, as indicated by two positive stool tests, was 54.3% in the daily group and 62.2% in the weekly group. We conclude that for the complete sample of subjects, the treatment effect of daily compared with weekly supplementation was similar under conditions resembling a normal antenatal care program. *Am J Clin Nutr* 1996;63:000-000.

**KEY WORDS** Anemia, iron, pregnancy, weekly supplementation

## INTRODUCTION

Iron-deficiency anemia is an important nutritional problem in developing countries (1). Pregnant women are at special risk and the prevalence of anemia for this population category in Southeast Asia is as high as 60-70% (2, 3). This is primarily because the amount of dietary iron absorbed is often too small to meet the increased demands during pregnancy for expanded red cell mass in the mother and iron deposition in the products of conception. Because anemia is associated with poor pregnancy outcome (4, 5), many countries have started programs that attempt to increase iron intake during pregnancy by distributing iron tablets to pregnant women. The tablets are usually distributed through the public health system, with the recommendation that women should take the tablets daily throughout the second and third trimester of pregnancy (6).

Despite these large-scale programs, the prevalence of anemia has not decreased in the past decade (2, 6). The main factors that influence the efficacy of the iron-supplementation programs are inefficient health services and low compliance of the pregnant women (6-8). Compliance is influenced by the undesirable side effects of the ingested iron, which are related to

the amount (9), to the form (8), and possibly also to the frequency of supplement ingestion.

Studies in rats have shown that administration of iron supplements every third day is as effective in improving iron status as daily supplementation (10, 11). It is argued that when the administration of iron is matched with the intestinal mucosal renewal time, the absorption and retention of the iron is more efficient (11). This higher absorption of iron when given on a once-a-week basis could, however, not be confirmed in non-anemic American women (12). On the other hand, studies in anemic Indonesian populations—preschool children (13) and nonpregnant women (14)—did demonstrate similar effectiveness of weekly compared with daily supplementation in restoring hemoglobin concentrations.

Supplementation on a weekly instead of daily basis would have important implications for the organization and efficiency of iron-supplementation programs for pregnant women. Therefore, it was the aim of this study to compare daily supplementation, ie, the current practice for pregnant women in Indonesia, with weekly supplementation. We attempted to compare the weekly and daily supplementation under conditions similar to the ongoing antenatal care program, and to cause as little disturbance to the normal conditions of the current iron-supplementation program as possible.

## SUBJECTS AND METHODS

### Subjects

The study was carried out from January to May 1995 in the rural district of Tangerang, West Java. Subjects were pregnant women in their 8th to 24th week. We sought to have ≥ 50 anemic, pregnant women in each treatment group because this number would allow us to distinguish a differential change in

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110

Folate

what about folic acid needs in 1st trimester 77

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Duplicate Method

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hemoglobin concentration of 5 g/L between groups with a 5% significance level and a power of 80%, even allowing for 15% attrition. Subjects were selected at six health centers serving 90 small villages with similar socioeconomic characteristics. These health centers provide prenatal care, including free distribution of iron tablets, to all pregnant women from their first visit onward. All pregnant women who came to one of the six health centers for the first prenatal care check-up of their current pregnancy were asked to participate in the study. A total of 176 subjects were selected, 70.5% of whom had a hemoglobin concentration < 110 g/L, which is used as a general indicator for anemia during pregnancy (3).

The research proposal was approved by the Ethical Review Committee of the Regional SEAMEO-TROPED Center for Community Nutrition at the University of Indonesia, Jakarta.

Methods

Random allocation to one of two treatment groups was done on the basis of the health center each woman attended. All women from three health centers, chosen at random, were allocated to the daily group (n = 90), whereas all women from the remaining three health centers were allocated to the weekly group (n = 86). This allocation method was chosen for practical reasons to avoid confusion among health center staff and subjects. Daily supplements were tablets containing 60 mg elemental Fe as ferrous sulfate and 0.25 mg folic acid for ingestion every day of the week. This schedule and dosage is the norm in Indonesia (8). The weekly group ingested tablets similar to those of the daily group, but the subjects were instructed to take two tablets (one in the morning and one in the afternoon), containing in total 120 mg elemental Fe and 0.50 mg folic acid, once a week. Considering the high prevalence of low hemoglobin values, no placebo group was included because of ethical reasons.

To evaluate the effect of the two treatments two blood samples were drawn from each subject. The first sample was collected during the subjects' first visit to the health center immediately before the women received their iron tablets. The second sample was collected when the women were 28-32-wk pregnant. This timing was chosen to allow the hemoglobin concentration to increase (15), and to head off the high dropout rate that we found previously (7) when we attempted to take follow-up blood samples in the last month of pregnancy. The duration of supplementation was therefore not the same for each woman, but varied from 8 to 20 wk (Figure 1).

The tablets were distributed by the midwives of the local health posts once a month, as is normal practice in the ongoing supplementation program. To optimize compliance, each subject was instructed thoroughly and the midwives kept special cards to record the number of tablets distributed. Compliance was checked by asking the subjects how many tablets they had ingested. Furthermore, we attempted to collect two stool samples from each subject to check compliance by using a simple test for fecal iron (16). The normal practice of the ongoing iron-supplementation program was disturbed as little as possible.

Venous blood samples (5 mL) were collected in tubes without anticoagulant between 0900 and 1100 (~3 h after breakfast). Because we could not maintain cold preservation, specifically for hemoglobin, from these remote locations, a temporary dry preservation method was used (17). Immedi-

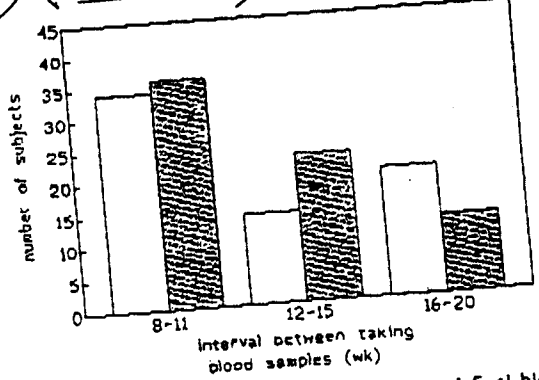


FIGURE 1. Distribution of time between initial and final blood sampling for the groups supplemented daily (n = 68) and weekly (n = 71).

ately after venipuncture, 0.02 mL blood was collected with a micropipette and transferred onto filter paper (Whatman no. 1; Balston Ltd, Maidstone, United Kingdom). The blood spots were collected in duplicate. These samples were air-dried for ≥ 30 min and put into small plastic bags. Hemoglobin analysis was carried out within 1 wk after sample collection. Before assay, the paper was soaked in 5 mL Drabkin solution for ~6 h until all the blood was extracted, then hemoglobin was determined by the cyanomethemoglobin method (17) (Merck-test 3317; Merck, Darmstadt, Germany). The within-assay variability, based on duplicate measurements, was ± 2.3 g/L. Previous tests showed that the difference between average hemoglobin values of 105 blood samples as determined by the filter-paper method compared with fresh blood was 1.6% (unpublished data from the Bogor Nutrition Institute, where the present analysis was also carried out). No correction was made for this difference in the reported data. For serum ferritin, blood was allowed to clot before it was put in a cool box and taken to the laboratory. After arrival at the laboratory, the samples were centrifuged for 10 min at room temperature, and the serum was separated within 6 h of blood collection and stored at -20 °C until analyzed. After the final blood collection was finished, serum ferritin was determined in all samples by enzyme immunoassay (17) using a commercial kit (IMX System; Abbott, Abbott Park, IL). Duplicate analyses were performed for 12% of the samples, and within-run variability was 0.31 µg/L. Each run included manufacturer-provided control sera with ferritin concentrations of 20 and 150 µg/L. Results of a run were only considered valid if results for the respective control sera were within the limits of 16-24 and 120-180 µg/L. Stool samples were collected in small plastic containers, transported in a cool box, and stored at 4 °C in the laboratory where they were analyzed within 1 wk. At baseline, a stool sample was collected to determine the presence of intestinal parasites (18).

Body weight was measured to the nearest 0.1 kg with an electronic weighing scale (SECA 770 alpha; SECA, Hamburg, Germany). Body height was measured to the nearest 0.1 cm by using a microtoise.

Statistical analysis

Treatment effects in the two groups were compared by using the multivariate analysis of variance (MANOVA) repeated-

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measures design of SPSS/PC+ (SPSS Inc, Chicago) (19) with the two treatment types (daily compared with weekly supplementation) as a between-subjects factor and treatment effect (start and finish of supplementation) as a within-subjects factor. Between-group differences in treatment effect would be indicated by a significant interaction between treatment effect and treatment type. Initial hemoglobin and serum ferritin concentrations were included in the analysis as between-subjects factors to correct for their possible confounding influence. Helminthic infestation and duration of supplementation were included in the analysis as covariants to test their influence on changes in blood variables. Serum ferritin values were not normally distributed and were analyzed after a natural logarithm transformation that normalized the distributions.

## RESULTS

Of the 176 women initially enrolled, a complete set of data was obtained for 68 women in the group supplemented daily and 71 women in the group supplemented weekly (Table 1). Attrition occurred for several reasons: 15 women refused a second blood collection ( $n = 9$  daily,  $n = 6$  weekly); 9 women changed residence ( $n = 5$  daily,  $n = 4$  weekly); 8 women delivered before they could be reached for the second blood sampling ( $n = 5$  daily,  $n = 3$  weekly); 3 women had a premature delivery ( $n = 2$  daily,  $n = 1$  weekly); 1 woman from the daily group had a miscarriage; and 1 woman from the weekly group became ill. No significant differences existed between treatment groups for the reasons for dropping out, and the dropouts had characteristics similar to those who completed the study.

The distribution of intervals between initial and final blood sampling was not significantly different between groups (Figure 1). No significant differences existed between the treatment groups in terms of age, weight, gestational date, number of past pregnancies, and duration of supplementation, but the women in the group supplemented daily were taller and the interval between their current and last pregnancy was longer when the total samples were compared ( $P < 0.05$ ) (Table 1).

At baseline, 66.2% of the women in the daily group ( $n = 68$ )

76.1% of the weekly group ( $n = 71$ ) had hemoglobin concentrations  $< 110$  g/L (NS). Of the women who were in the first trimester of pregnancy, 64.3% of the daily and 63.2% of the weekly group were anemic, with a hemoglobin concentra-

tion  $< 110$  g/L. Of the women in the second trimester ( $n = 49$ ), 44.9% of the daily and ( $n = 57$ ) 64.9% of the weekly group had hemoglobin  $< 105$  g/L ( $P = 0.04$ ), which was suggested to be a more precise indicator for anemia during the second trimester of pregnancy (20). At baseline, 44.1% and 22.1% of women supplemented daily had serum ferritin values  $< 20$  and  $12$   $\mu\text{g/L}$ , respectively (21); for the women supplemented weekly these prevalences were 53.5% and 36.6%, respectively. Hemoglobin concentrations were  $< 110$  g/L and serum ferritin concentrations were  $< 20$   $\mu\text{g/L}$  in 33.8% of the group supplemented daily and in 47.9% of the group supplemented weekly. Of the women with a hemoglobin concentration  $< 110$  g/L, those supplemented daily ( $n = 45$ ) were significantly older, were taller, had a higher number of past pregnancies, and had a longer interval between the current and past pregnancy compared with the group supplemented weekly ( $n = 54$ ).

Although the women were randomly allocated to a treatment group based on health center attendance, there was a significant difference of 4 g/L ( $P = 0.01$ ) in initial hemoglobin concentrations between groups (Table 2). The initial serum ferritin concentrations were also higher in the group supplemented daily, although this difference was not significant ( $P = 0.055$ ). At the end of the study, no significant difference in hemoglobin concentration still existed between groups, but the serum ferritin concentration was higher in the group supplemented daily ( $P = 0.01$ ). Hemoglobin concentration at the end of the study was significantly higher ( $P < 0.001$ ) than at baseline for both groups by repeated-measures statistics, but there were no significant within-group changes in serum ferritin.

The changes in hemoglobin and serum ferritin were related to the initial concentrations of these variables:  $r = -0.65$  ( $P = 0.001$ ) for hemoglobin and  $r = -0.45$  ( $P = 0.001$ ) for serum ferritin. Therefore, to evaluate the differences in treatment effect between the two groups, the initial concentrations of hemoglobin and serum ferritin had to be taken into consideration as possible confounders because these concentrations differed between the treatment groups. This was done by dividing initial hemoglobin concentrations into three and serum ferritin concentrations into four, approximately equal-sized categories (Table 3). These concentration categories were included in the repeated-measures analysis of variance as between-subjects factor. Furthermore, the duration of supplementation was included in the repeated-measures analysis as a covariant to evaluate whether the duration influenced

TABLE 1

Selected characteristics of subjects at the beginning of the study<sup>1</sup>

	Supplemented daily		Supplemented weekly	
	Total sample ( $n = 68$ )	Anemic subsample ( $n = 45$ )	Total sample ( $n = 71$ )	Anemic subsample ( $n = 54$ )
Age (y)	26.2 $\pm$ 5.7	26.5 $\pm$ 5.6 <sup>2</sup>	25.0 $\pm$ 5.3	24.4 $\pm$ 5.0
Gestational date (wk)	17.5 $\pm$ 4.8	17.6 $\pm$ 4.8	18.6 $\pm$ 5.3	19.2 $\pm$ 5.3
Weight (kg)	49.2 $\pm$ 7.5	48.5 $\pm$ 6.1	47.3 $\pm$ 6.4	46.8 $\pm$ 6.5
Height (cm)	150.7 $\pm$ 4.5 <sup>3</sup>	150.6 $\pm$ 4.8 <sup>3</sup>	148.3 $\pm$ 4.5	148.0 $\pm$ 4.4
Past pregnancies ( $n$ )	3.5 $\pm$ 2.3	4.0 $\pm$ 2.5 <sup>2</sup>	2.8 $\pm$ 2.1	2.8 $\pm$ 2.1
Interval since last pregnancy (mo)	41.0 $\pm$ 33.2 <sup>2</sup>	41.6 $\pm$ 29.8 <sup>2</sup>	29.5 $\pm$ 32.0	25.9 $\pm$ 29.2
Duration of supplementation (wk)	11.5 $\pm$ 4.0	11.1 $\pm$ 3.9	11.2 $\pm$ 3.6	10.8 $\pm$ 3.5

<sup>1</sup>  $\bar{x} \pm \text{SD}$ .<sup>2,3</sup> Significantly different from group supplemented weekly: <sup>2</sup>  $P < 0.05$ , <sup>3</sup>  $P < 0.01$ .

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TABLE 2  
Hematologic values at the beginning and end of the supplementation period<sup>1</sup>

Study group	Beginning		End	Difference
	Supplemented daily (n = 68)	106 ± 9 <sup>2</sup>	110 ± 7	4 ± 9 <sup>3</sup>
Hemoglobin (g/L)	28.0 ± 19.2 [21.9]	27.7 ± 19.8 [21.5] <sup>2</sup>		
Serum ferritin (µg/L)				
Supplemented weekly (n = 71)	102 ± 10	108 ± 8	6 ± 8 <sup>3</sup>	-2.7 ± 13.4
Hemoglobin (g/L)	23.2 ± 20.5 [17.1]	20.5 ± 16.9 [15.6]		
Serum ferritin (µg/L)				

<sup>1</sup> Arithmetic mean ± SD; geometric mean in brackets.

<sup>2</sup> Significantly different from the related value in group supplemented weekly, P = 0.01.

<sup>3</sup> Significant within-group increase from beginning to end, P = 0.001.

changes in blood variables. The gestational date at baseline was not included in the analysis because it was directly related to the duration of supplementation (r = -0.92). The differences between treatment effects between groups (tested by the interaction between treatment type and effect) for hemoglobin (P = 0.609) and serum ferritin (P = 0.127) were not significant (Tables 2 and 3). Therefore, the effects of daily compared with weekly supplementation were similar in the complete group of subjects. The duration of supplementation did not have a significant effect on changes in hemoglobin (P = 0.310) or serum ferritin (P = 0.744). The most important factor influencing the changes in hemoglobin and serum ferritin were their concentrations at baseline, the lowest baseline concentrations led to larger changes (P < 0.001, interaction between treatment effect and initial hematologic class).

At the end, the prevalence of anemia (hemoglobin < 110 g/L) had decreased in similar fashion in both groups to 45.6% of the women supplemented daily and to 56.3% of the women supplemented weekly. The percentage of women with serum ferritin concentrations < 20 µg/L did not change and was 47.1% for daily and 63.4% for weekly supplemented groups, respectively. The prevalences for serum ferritin concentrations < 12 µg/L were 22.1% and 29.4% for women supplemented daily and weekly, respectively.

To further study the treatment effect, data for the subgroup women with initial hemoglobin values < 110 g/L are pre-

sented in Table 4. At the start, both hemoglobin and serum ferritin concentrations were significantly higher in the women supplemented daily than in the women supplemented weekly. Hemoglobin concentration increased by 8 g/L in both groups (P < 0.01). There was no difference in treatment effect between groups (tested by the interaction between treatment type and effect) for hemoglobin (P = 0.705) (Table 3). There were no significant within-group changes in serum ferritin concentration. A small decrease in the weekly group together with a small increase in the daily group, however, caused a small but significant between-group difference in treatment effect (P = 0.049). Also, for the subgroup of women with low hemoglobin concentrations at baseline, the duration of supplementation did not significantly influence the changes in blood variables.

Differences in the prevalence of intestinal parasites, especially hookworm, could also have influenced the treatment effect. Stool samples for 82 of 139 women were collected at the start of the study for the diagnosis of parasites: 42 from women in the group supplemented daily and 40 from women in the group supplemented weekly. There was no difference in hookworm prevalence between groups: 28.5% of daily and 32.5% of weekly supplemented women were infected. When infestation with hookworm was entered as a factor in the analysis of variance, there was no significant difference in the treatment effect between groups for hemoglobin or serum ferritin.

(74)

hookworm

†

TABLE 3  
Results of repeated-measures ANOVA and ANCOVA: hematologic indexes by treatment effect, treatment type, and initial hemoglobin or serum ferritin concentration<sup>1</sup>

	All subjects		Anemic subjects	
	Hemoglobin	Ferritin	Hemoglobin	Ferritin
Within subjects				
Treatment effect (time)	0.000	0.246	0.000	0.372
Between subjects				
Treatment type (daily vs weekly)	0.246	0.07	0.109	0.016
Initial hematologic class <sup>1</sup>	0.000	0.000	0.000	0.000
Interactions				
Treatment type × hematologic class	0.255	0.44	0.167	0.483
Treatment effect × type	0.609	0.127	0.705	0.049
Treatment effect × hematologic class	0.000	0.000	0.001	0.001
Treatment effect × type × hematologic class	0.356	0.526	0.500	0.498
Covariant				
Duration of supplementation	0.310	0.744	0.296	0.635

<sup>1</sup> Hematologic classes were made as follows: hemoglobin (g/L): <100 (n = 40), 100-110 (n = 59), ≥110 (n = 40); serum ferritin (µg/L): <12 (n = 41), 12-20 (n = 28), >20-30 (n = 30), >30 (n = 40).

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TABLE 4  
 Hematologic values at the beginning and end of the supplementation period for the women with hemoglobin concentrations <110 g/L at the beginning<sup>1</sup>

Study group	Beginning	End	Difference
Supplemented daily (n = 45)			8 ± 8 <sup>1</sup>
Hemoglobin (g/L)	101 ± 6 <sup>2</sup>	109 ± 7	2.5 ± 16.4 <sup>3</sup>
Serum ferritin (μg/L)	24.7 ± 17.6 [19.4] <sup>2</sup>	27.3 ± 20.1 [20.9] <sup>4</sup>	
Supplemented weekly (n = 54)			8 ± 7 <sup>1</sup>
Hemoglobin (g/L)	98 ± 8	106 ± 7	-1.6 ± 11.9
Serum ferritin (μg/L)	18.7 ± 14.0 [14.5]	17.1 ± 12.5 [13.8]	

<sup>1</sup> Arithmetic mean ± SD; geometric mean in brackets.

<sup>2</sup> Significantly different from group supplemented weekly; <sup>3</sup> P < 0.05; <sup>4</sup> P < 0.01.

<sup>5</sup> Significant within-group increase from beginning to end, P < 0.01.

<sup>6</sup> Significantly different from group supplemented weekly, after correction for serum ferritin concentration at the beginning, indicated by treatment effect.

× type interaction, P = 0.049 (see Table 3).

Compliance with supplement intake was checked in two ways (Table 4). First, at the second blood sampling, women were asked whether they had taken all tablets given to them. In the group supplemented daily, 48.5% of women claimed that they had taken all tablets, whereas 63.4% of the weekly group so claimed (P = 0.08). Second, we had planned to collect a small amount of stool from all subjects after 4 wk and at the end of supplementation; we were able to collect samples from 95 women after 4 wk and from 105 at the end of the study (Table 5). These stool samples were checked for the presence of elemental iron. The stool tests did not indicate a significant difference in compliance between the two groups (Table 5). Stools of 72 women were collected on both occasions, and 58.3% of these women had positive stool samples on both occasions. The hemoglobin concentration of the women with two positive stool samples increased by 11 ± 7 g/L in the daily group (n = 19, initial hemoglobin 103 ± 7 g/L) and by 10 ± 7 g/L in the weekly group (n = 20, initial hemoglobin 99 ± 7 g/L) (P = 0.54; after correction for initial hemoglobin and duration of supplementation). Serum ferritin changed by 3.9 ± 7 μg/L (P = 0.38) for the daily group and -1.2 ± 9.3 μg/L for the weekly group (between-group difference after correction for initial concentration: P = 0.02).

The duration of supplementation was negatively associated with compliance. Of the women who were supplemented < 12 wk, 67.1% claimed to have taken all tablets, whereas 44.1% of women who were supplemented longer than 12 wk so claimed (P = 0.01). Overall, 17.3% (n = 24) of all women complained

about adverse side effects, with the percentage being similar in both groups (16.2% in the daily group, 18.3% in the weekly group). Side effects influenced compliance. Of those women complaining about side effects only 20.8% claimed to have taken all tablets, whereas 63.5% of women who did not complain claimed to have taken all tablets. No specific information was collected about types of side effects.

DISCUSSION

Pilot studies have shown that the high prevalence of anemia among pregnant women in developing countries might be reduced by distributing iron tablets to all pregnant women through the public health system (9). In practice, however, the efficiency of large-scale supplementation programs has been limited for various reasons. Women in developing countries often do not come to the health centers until late in pregnancy. When they do, the health centers may not have sufficient supplies of iron supplements or may not be consistent in providing the supplements. Even when provided with enough iron tablets for daily ingestion during the remainder of the pregnancy, the tablets are often ignored or taken only erratically (6-8, 22). Alternative strategies to reduce the rate of anemia are therefore urgently needed.

This study aimed to study the effect of daily compared with weekly iron supplementation in pregnant women. The advantages of weekly supplementation would be reduced costs and possibly better compliance. The study conditions resembled the usual conditions of the official supplementation program now administered by the Indonesian Ministry of Health as much as possible: all pregnant women who visited the health center for the first time were eligible, supplement ingestion was not strictly supervised, and the tablets were the same as those used by the official program. Hence, the results of our study can be interpreted as demonstrating efficacy in a situation as close as possible to "real life". Because the women in the group supplemented daily received tablets under usual conditions, the comparison of the effect of the weekly and daily doses is valid in terms of relative effectiveness. However, the extent of the difference in iron status due to the treatment may have been different if we had strictly supervised tablet ingestion.

Both treatments resulted in similar and significant increases in hemoglobin concentration, but serum ferritin did not show any significant concentration changes in the whole sample of

TABLE 5  
 Compliance with supplement ingestion as assessed by stool test for elemental iron two times during the study<sup>1</sup>

Study group	Time of stool collection		Both 4 wk and end <sup>2</sup>
	4 wk	End	
	%		
Supplemented daily (n = 68)	68.8 [48]	57.1 [49]	54.3 [35]
Supplemented weekly (n = 71)	74.5 [47]	62.5 [56]	62.2 [37]
Total (n = 139)	71.6 [95]	60.0 [105]	58.3 [72]

<sup>1</sup> Percentage of subjects with iron in stool; n in brackets.

<sup>2</sup> Percentage of subjects with iron in stool on both occasions.

6

1

*Can we expect 8-10 g/L increase?*

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subjects. Of the women with initial hemoglobin concentrations < 110 g/L, the average increase in hemoglobin was 8 g/L in both groups. In these women a significant between-group difference was noted in the serum ferritin changes, but the within-group changes over time were small and not statistically nor biologically significant. Anemic, pregnant Indonesian women who were supplemented under supervision during a relatively short period of 8 wk with 60 mg Fe/d showed increases in hemoglobin similar to those of our anemic subjects, and the reported changes in serum ferritin were similar to the changes in our group that was supplemented daily (23). Similar changes occurred among pregnant Sri Lankan women who received supplements under program conditions (24).

The best estimation of the true treatment effect, that which could have occurred if subjects had actually ingested all tablets given to them, is estimated from the results of women who had large amounts of iron in their stool on two occasions. In these women, there was no significant difference between groups for hemoglobin response, which increased by 10–11 g/L in each group. For women with two positive stool samples in the daily group, a nonsignificant increase in serum ferritin of  $\approx 4 \mu\text{g/L}$  occurred, but because of a small decrease in the weekly group, the difference between groups of  $5 \mu\text{g/L}$  was significant ( $P = 0.02$ ).

It can be concluded that both treatments resulted in similar significantly improved hemoglobin concentrations. Iron stores, as indicated by serum ferritin, were not significantly improved by either daily or weekly supplementation when analyzed for the whole study population. Considering the low dose of iron given weekly, and the relatively short period of supplementation, the results in the group supplemented weekly stand in contrast with the current recommendations that 120 mg Fe/d should be taken throughout the second half of pregnancy (25). This effect can only be explained by efficient iron absorption when taken on a weekly basis. Assuming 4.2 L blood in the present subjects (26), 3.34 mg Fe/g hemoglobin (27), and a daily requirement of 4 mg Fe (28), the following calculation can be made. To increase hemoglobin by 10 g/L during a period of 11 wk by supplementing with 120 mg Fe, in total (as presumably occurred in women with two positive stool samples), the iron-absorption rate from the weekly supplement would be  $\approx 22\%$ , assuming a daily dietary iron uptake of 2 mg (29, 30). Absorption rates  $> 20\%$  have been reported for women in the second or third trimester of pregnancy, when taking a small water-dissolved dose of iron 30 min before breakfast was consumed (31).

Intermittent supplementation was shown to have an efficiency similar to that of daily supplementation in rats (10, 11), children (13), and nonpregnant women (14). It is thought that when iron supplements are ingested only once during the life cycle of the intestinal mucosa cells that the rate of absorption is higher (10, 11). Furthermore, in rats the retention of iron was better with supplementation every 3 d than on a daily basis (11). The results of the present study support these previous findings. On the other hand, higher absorption rates of iron with weekly compared with daily supplementation could not be confirmed in a laboratory-based study in women (12). However, this study was conducted in well-nourished American women, whose need for efficient iron absorption is much lower compared with the needs of the Indonesian subjects from the present and previous studies (13, 14); this may be a reason for

the conflicting results. Furthermore, the laboratory-based study was shorter in duration.

Weekly supplementation—compared with daily supplementation—may result in better compliance with tablet intake, because women experience negative side effects less often. More women in the group supplemented weekly (63.4%) than in the group supplemented daily (48.5%) claimed to have taken all tablets, although this difference was not significant ( $P = 0.08$ ). No trend toward differential compliance, however, could be confirmed by the stool tests for elemental iron. An underestimation of true compliance for the group supplemented weekly might have occurred, however, because we could not be certain that the women presented a stool sample on the day immediately following the day of supplement ingestion. Furthermore, we observed that compliance, as claimed by the women, was higher in those who took tablets for  $< 12$  wk compared with those who took supplements longer than 12 wk. This declining compliance rate may have influenced the fact that the duration of supplementation was not associated with changes in hemoglobin concentration. Generally, we conclude that compliance in this study was higher than reported in previous studies among pregnant Indonesian women (7, 20).

In summary, we conclude that supplementation of pregnant women once per week with 120 mg Fe and 0.50 mg folic acid was as effective as daily supplementation with 60 mg Fe and 0.25 mg folic acid in terms of hematologic response under conditions resembling routine antenatal care. If the two regimens are biologically equivalent, then clearly weekly supplementation would be economically advantageous, and distribution and monitoring might be possible at a community level instead of requiring medical service staff in each instance. Another positive effect of weekly supplementation could be that the adverse interactive effect of large amounts of iron on the absorption of other micronutrients, such as zinc, would be reduced (32). Our findings, however, await confirmation in other ethnic and geographic settings. Furthermore, studies with other types of supplements (33), including combined supplementation of iron and vitamin A (23), should be carried out.

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## REFERENCES

1. Yip R. Iron deficiency: contemporary scientific issues and international programmatic approaches. *J Nutr* 1994;124(suppl):1479S–90S.
2. United Nations ACC/SCN. Second report on the world nutrition situation. Vol 1. Global and regional results. Geneva: ACC/SCN, 1992.
3. World Health Organization. The prevalence of anemia in women: a tabulation of available information. 2nd ed. WHO/MCH/MSM 92.2. Geneva: WHO, 1992.
4. Schoff TO, Hediger ML, Fischer RL, Shearer JW. Anemia vs iron deficiency: increased risk of preterm delivery in a prospective study. *Am J Clin Nutr* 1992;55:985–8.
5. Murphy JF, Newcombe RG, O'Riordan J, Colles EC, Pearson JF. Relation of hemoglobin levels in first and second trimesters to outcome of pregnancy. *Lancet* 1986;1:992–4.
6. ACC/SCN. Controlling iron deficiency. ACC/SCN state-of-the-art

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series. Geneva: ACC/SCN, 1991. (Nutrition policy discussion paper no. 9.)

7. Schultink W, van der Ree M, Matulessi P, Gross R. Low compliance with an iron-supplementation program: a study among pregnant women in Jakarta, Indonesia. *Am J Clin Nutr* 1993;57:135-9.
8. Bonnar J, Goldberg A, Smith JA. Do pregnant women take their iron? *Lancet* 1969;457-8.
9. Charoenlarp P, Dhanamitta S, Kaewwicht R, et al. A WHO collaborative study on iron supplementation in Burma and in Thailand. *Am J Clin Nutr* 1988;47:280-97.
10. Wright AJA, Southon S. The effectiveness of various iron-supplementation regimens in improving the Fe status of anaemic rats. *Br J Nutr* 1990;63:579-85.
11. Viteri FE, Xunian L, Tolomei K, Martin A. True absorption and retention of supplemental iron is more efficient when iron is administered every three days rather than daily to iron-normal and iron-deficient rats. *J Nutr* 1995;125:82-91.
12. Cook JD, Reddy MB. Efficacy of weekly compared with daily iron supplementation. *Am J Clin Nutr* 1995;62:117-20.
13. Schultink W, Gross R, Gliwitski M, Karyadi D, Matulessi P. Effect of daily vs twice weekly iron supplementation in Indonesian preschool children with low iron status. *Am J Clin Nutr* 1995;61:111-5.
14. Gross R, Schultink W, Juliawati. Treatment of anaemia with weekly iron supplementation. *Lancet* 1994;344:821.
15. Svanberg B, Arvidsson B, Norrby A, Rybo G, Sölvell L. Absorption of supplemental iron during pregnancy—a longitudinal study with repeated bone-marrow studies and absorption measurements. *Acta Obstet Gynecol Scand Suppl* 1975;48:87-103.
16. Affifi AM, Banwell GS, Bennison RJ, et al. Simple test for ingested iron in hospital and domiciliary practice. *Br Med J* 1966;1:1021-2.
17. International Nutritional Anemia Consultative Group. Measurements of iron status. Washington, DC: INACG, 1985.
18. World Health Organization. Basic laboratory methods in medical parasitology. Geneva: WHO, 1991.
19. Norusis MJ. SPSS/PC—advanced statistics 4.0. Chicago: SPSS Inc, 1995.
20. Centers for Disease Control and Prevention. CDC criteria for anemia in children and childbearing age women. *MMWR: Morbidity and Mortality Weekly Rep* 1989;38:400-4.
21. Hallberg L, Bengtsson C, Lapidus L, Lundberg PA, Hultén L. Screening for iron deficiency: an analysis based on bone-marrow examinations in a population sample of women. *Br J Haematol* 1993;85:787-98.
22. Thorand B, Schultink W, Gross R, Sastroamidjojo S, Wentzel S. Efficiency of the iron supplementation program for pregnant women in Jenepono, South Sulawesi, Indonesia. *Asia Pac J Clin Nutr* 1994;3:211-5.
23. Suharno D, West CE, Muhilal, Karyadi D, Hautvast JGAJ. Supplementation with vitamin A and iron for nutritional anemia in pregnant women in West-Java, Indonesia. *Lancet* 1993;342:3425-8.
24. Atukorala TMS, de Silva LDR, Dechering WHJC, Dassenaetke TSC, Perere RS. Evaluation of effectiveness of iron-folate supplementation and anthelmintic therapy against anemia in pregnancy—a study in the plantation sector of Sri Lanka. *Am J Clin Nutr* 1994;60:286-92.
25. DeMaeyer EM, Dallman P, Gurney JM, Hallberg L, Sood SK, Srikantia SG. Preventing and controlling iron deficiency anaemia through primary health care. Geneva: WHO, 1989.
26. Dacie JV, Lewis SM. Practical haematology. 7th ed. Edinburgh, United Kingdom: Churchill Livingstone, 1991.
27. Hallberg L, Hultén L, Bengtsson C, Lapidus L, Lindstedt G. Iron balance in menstruating women. *Eur J Clin Nutr* 1995;49:200-7.
28. Bothwell TH, Charlton RW, Cook JD, Finch CA. Iron metabolism in man. Oxford, United Kingdom: Blackwell, 1979.
29. Hunt JR, Gallagher SK, Johnson LK. Effect of ascorbic acid on apparent iron absorption by women with low iron stores. *Am J Clin Nutr* 1994;59:1381-5.
30. Hultén L, Gramatkovski E, Gleerup A, Hallberg L. Iron absorption from the whole diet. Relation to meal composition, iron requirements and stores. *Eur J Clin Nutr* 1995;49:794-808.
31. Whittaker PG, Lind T, Williams JG. Iron absorption during normal human pregnancy: a study using stable isotopes. *Br J Nutr* 1991;65:457-63.
32. Solomons NW. Competitive interaction of iron and zinc in the diet: consequences for human nutrition. *J Nutr* 1986;116:927-31.
33. Cook JD, Carraga M, Lahn S, Schultink W, Skitne BS. Gastric delivery system for iron supplementation. *Lancet* 1990;335:1246-9.