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Research Article
Impact of Weekly Versus Daily Iron-folic Acid Supplementation for Pregnant Women with Anemia on Hemoglobin Levels, Clinical Symptoms and Subjective Complaints

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Abstract

Background: Iron-Folic Acid (IFA) supplementation programs for pregnant women have been implemented for many years in Indonesia but the prevalence of anemia in pregnant women remains high largely due to low adherence to taking IFA tablets and side effects. **Objective:** This study aimed to investigate the low compliance with IFA supplementation in pregnant mothers with anemia and associated negative side effects. **Methodology:** The current study compared the effectiveness of short-term IFA supplementation in pregnant mothers given IFA weekly versus daily for 8 weeks using a pre- and post-test experimental design. Each IFA tablet contained 200 mg ferrous sulfate and 0.25 mg folic acid. The number of respondents in each group included 47 pregnant women with mild anemia. Hemoglobin (Hb) levels were analyzed using the cyanmethemoglobin method. **Results:** Mean Hb levels pretreatment were the same for both groups, as well as nutrition intake during treatment and socioeconomic conditions, such as education, family income and nutrition knowledge. Changes in Hb levels in the two treatment groups did not differ significantly ($p = 0.685$), although both groups had increased Hb levels (weekly, 0.5 g dL^{-1}; daily, 0.6 g dL^{-1}). Clinical symptoms and subjective complaints related to anemia and iron consumption also showed improvement in both treatment groups. **Conclusion:** It is concluded that short-term IFA supplementation whether given daily or weekly effectively increases Hb level in pregnant women with anemia and improves clinical symptoms, as well as subjective complaints.

Key words: Anemia, weekly IFA supplementation, pregnant women, dietary nutrients, iron deficiency

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The anemia prevalence among pregnant women in Indonesia remains high despite the implementation of Iron-Folic Acid (IFA) supplementation programs. The results of a recent national survey showed the prevalence of anemia was 37.1%, representing a public health problem that is approaching severe levels[1,2]. Anemia in pregnant women results in bleeding during childbirth and is a principal cause of maternal mortality in Indonesia[3].

In addition to adversely affecting maternal mortality, anemia in pregnant women also impacts the fetus. Some negative impacts include natural abortion, fetal death or stillbirth, neonatal death, congenital defects, fetal anemia and low birth weight infants[4]. One major cause of anemia in pregnant women is inadequate consumption of iron-rich food both in quality and quantity to supplement the increased demand for iron during fetal development and formation of new hemoglobin (Hb) in red blood cells[5]. In addition, anemia is also influenced by socioeconomic (education, occupation, income, anemia knowledge) and maternal (gestational age, time since last pregnant) factors.

Since the prevalence of anemia among pregnant women in Indonesia has been difficult to moderate, anemia prevention and control is considered a public health priority. The Indonesian government is trying to reduce the incidence of anemia and ensure that pregnant women have sufficient iron intake. Efforts to control anemia in pregnant women include long-term programs aimed at changing dietary patterns to improve nutrition and short- term programs involving IFA supplementation.

The results of a recent Indonesia health profile analysis indicated low compliance to IFA consumption among pregnant women[6]. This analysis found that only 36.3% of pregnant women took IFA tablets for 0-30 days while pregnant, 2.8% took IFA for 31-59 days, 8.3% took IFA for 60-89 days and 18% took IFA tablets for more than 90 days during their pregnancy (simply days in total during pregnancy). Furthermore, 19.3% of pregnant women did not consume IFA tablets at all. The low compliance with IFA consumption is largely due to its negative side effects (nausea, stomach pain, constipation) that present sooner and more apparently than the positive effects which are increased Hb and iron levels in the body and fetus[7]. The current study was conducted to investigate the low compliance with IFA supplementation in pregnant mothers with anemia in Indonesia and associated negative side effects.

MATERIALS AND METHODS

Design, location, population and subjects: The current pre and post-test study was conducted in the Ciomas Subdistrict of Bogor, Indonesia and included pregnant women with anemia over 18 years of age. Before the study began, Hb screening was conducted to determine each subject's anemia status. Subjects were split into two groups; the number of samples included in the current study was calculated based on a sample formula from a previous clinical trial that compared the means of the two groups[8]. The number of samples in each group were 47 pregnant women with anemia. Inclusion criteria consisted of pregnant women with mild anemia (Hb range, 9-10.9 g dL^{-1}) and a maximum gestation of 27 weeks[9]; exclusion criteria were pregnant women with moderate or severe anemia, blood in their sputum, urine and/or feces and those clinically suffering from chronic disease (e.g., protein energy deficiency; tuberculosis; liver, heart, or lung disease; diabetes mellitus and renal disorders).

Treatment: Although both groups were given the same dose of IFA per tablet, one group was given IFA once daily, while the other was given IFA once a week for a total of 8 weeks. The IFA tablets were government-supported and each contained 200 mg ferrous sulfate (equivalent to 60 mg of elemental iron) and 0.25 mg folic acid[10]. Each pregnant woman was routinely visited once a week and either given 7 IFA tablets for daily or 1 tablet for weekly ingestion. Each woman was given a form to record tablet consumption. During the weekly visit, an enumerator recorded the number of tablets consumed or remaining. Other dietary nutrient intake data was obtained using the 24 h recall method. Patients were excluded from the current study if they did not consume the tablet for 3 consecutive days (daily group) or weeks (weekly group).

Analysis: The Hb levels were analyzed using the cyanmethemoglobin method[11]. The Hb measurements were completed before and after the 8 week intervention period. The results of the 24 h recall method were analyzed using a NutriSurvey to obtain descriptions and adequate intake amounts of other dietary nutrients. The collected data was processed using a normality test, paired t-test and independent t-test.

RESULTS

Initial Hb screening was conducted on 149 pregnant women. Of these, 104 (69.8%) met inclusion criteria and

were willing to voluntarily follow the entire treatment plan. Then, the subjects were divided into two groups, each consisting of 52 pregnant women with anemia. By the end of the 8 week treatment, a total of 10 subjects (9.6%) had dropped out because they gave birth (4 women), moved away and were unreachable by researchers (3 women), or resigned due to health matters (3 women). Normality tests showed that initial Hb levels in both groups were normally distributed. Mean±Standard Deviation Hb pretest levels did not significantly differ between the treatment groups (weekly, 9.9±0.54 g dL^{-1}; daily, 10.0±0.59 g dL^{-1}; $p = 0.153$).

Characteristics of pregnant women with anemia: The frequency distribution of all subject characteristics at pretreatment showed statistical similarities between the two groups ($p>0.05$). Subjects were of childbearing age with a mean gestation of about 20 weeks (entering the second trimester). Approximately two-thirds of women were previously pregnant more than 2 years prior and the largest parity group was 1-4. In terms of socioeconomic variables, most women finished primary school, were not working, of lower economic status and had a low level of nutritional knowledge. Those with an occupational status routinely worked outside their home as factory laborers. Most subjects' incomes were lower than the minimum wage and were divided into three sections (tertile): Low, medium and high. Nutritional knowledge was also divided into three sections based on the number of correct answers on the NutriSurvey: less (<60% correct), adequate (60-80% correct) and good (>80% correct) (Table 1).

Nutrition intake: Table 2 shows that intake of most dietary nutrients was below the recommended dietary values. Energy, protein and vitamin C intake levels were about

Table 1: Frequency distribution of subject characteristics

	Weekly supplementation		Daily supplementation	
Variables	n	%	n	%
Age				
<20 years old	4	8.5	5	10.6
20-30 years old	30	63.8	29	61.7
>30 years old	13	27.7	13	27.7
Education				
Not completed primary school	37	78.7	30	63.8
Graduated from junior/senior high school	7	14.9	16	34.0
Graduated from the Academy/university	3	6.4	1	2.2
Occupation				
Employed	5	10.6	7	14.9
Unemployed	42	89.4	40	85.1
Family income				
Low	39	83.0	39	83.0
Middle	8	17.0	8	17.0
High	-	-	-	-
Nutrition knowledge				
Less (<60%)	35	74.5	39	82.9
Adequate (60-80%)	6	12.8	7	14.9
Good (>80%)	6	12.8	1	2.2
Gestation				
1st Trimester (<12 weeks)	9	19.1	10	21.3
2nd Trimester (13-24 weeks)	28	59.6	29	61.7
3rd Trimester (25-27 weeks)	10	21.3	8	17.0
Time since of last pregnancy				
<2 Years	15	31.9	18	38.3
>2 Years	32	68.1	29	61.7
Parity				
0	13	27.7	10	21.3
1-4	31	65.9	32	68.1
>4	3	6.4	5	10.6

Values are statistically non-significant at $p>0.05$

half the recommended value and dietary iron consumption apart from supplementation was very low (20%). The mean consumption of energy, protein and iron in both treatment groups was similar (NS), while the consumption of vitamin C in the weekly group was slightly higher than the daily group.

Hb levels: Weekly and daily groups showed significantly increased Hb levels pre- and post-test ($p<0.05$); weekly group levels increased by 5.1% ($p = 0.005$), while daily group levels increased by 6% ($p = 0.001$). However, these increases were not statistically significant between the two treatment groups ($p = 0.685$) (Table 3).

Clinical symptoms: Table 4 shows improvement of all clinical anemia symptoms in weekly and daily groups.

Subjective complaints: Table 5 shows improvement in all subjective complaints associated with anemia in both weekly and daily groups.

Table 2: Mean nutrient intake

Nutrients	Weekly supplementation (%)	Daily supplementation (%)
Energy	54.5	55.2
Protein	65.5	66.3
Iron	20.1	22.6
Vitamin C	62.6	50.2

Values are statistically non-significant at $p>0.05$

DISCUSSION

The current study was conducted to investigate the high prevalence of anemia among pregnant women in Indonesia[1] and low adherence to IFA supplement consumption[6]. Unfortunately, the various forms of nutritional education delivered to pregnant women in Indonesia, in addition to free IFA supplement distribution, has not sufficiently reduced the prevalence of pregnant women with anemia. Therefore, additional strategies are needed. The results of the present study contribute to current knowledge about supplement intake habits and represent an alternative to daily IFA supplementation. Weekly IFA supplementation is expected to reduce costs and improve intake compliance, a major factor determining a successful response to IFA supplementation among anemia patients[12,13].

The government-supported IFA tablets administered herein contain the equivalent of 60 mg of elemental iron in

Table 3: Hemoglobin levels before and after treatment

Parameters	Weekly supplementation	Daily supplementation	p-value
Baseline (g dL^{-1})	9.9±0.54	10.0±0.59	
Endline (g dL^{-1})	10.4±1.02	10.6±0.99	
Difference (g dL^{-1})	0.5	0.6	
Difference (%)	5.1	6.0	
p-value	0.005[1]	0.001[1]	0.685[2]

Supplementation values presented as Means±SD, [1]Within group comparison, [2]Between group comparison

Table 4: Clinical symptoms before and after treatment

	Weekly supplementation				Daily supplementation			
	Baseline		Endline		Baseline		Endline	
Indicators	n	%	n	%	n	%	n	%
Pale face	11	23.4	5	10.6	8	19.1	2	4.3
Pale eyes	25	53.2	12	25.5	20	42.6	11	23.4
Pale lips	9	19.1	3	6.4	12	25.5	4	18.5
Pale tongue	12	25.5	5	10.6	15	31.9	7	14.9
Pale palms	12	25.5	5	12.8	17	36.2	4	8.5
Pale nails	5	10.6	3	6.4	7	14.9	3	6.4

Between group comparison values are statistically non-significant at $p>0.05$

Table 5: Subjective complaints before and after treatment

	Weekly supplementation				Daily supplementation			
	Baseline		Endline		Baseline		Endline	
Indicators	n	%	n	%	n	%	n	%
Nausea, vomit	15	31.9	3	6.4	12	25.5	2	4.3
Dizziness	17	36.2	3	6.4	23	48.9	5	10.6
Limp	18	38.3	7	14.9	25	53.2	7	14.9
Numbness (feet, hand)	21	44.7	6	12.8	30	63.8	3	6.4

Between group comparison values are statistically non-significant at $p>0.05$

the form of ferrous sulfate, which is appropriate for treatment of iron deficiency in anemic patients. The tablet coating is intended to prevent oxidation of the iron, as well as mask its taste. Ferrous sulfate is also one of the most inexpensive and accessible forms of supplemental iron recommended by public health programs[14].

Anemia among pregnant women in Indonesia is not only due to an iron deficiency but also due to a lack of other nutrients that play a role in the absorption of iron and Hb formation[15]. Inadequate consumption of energy and other nutrients is often the result of low income, which prohibits people from obtaining good quality food in sufficient quantities. Low levels of education and nutritional knowledge also lead to selection of food with less nutritional quality. For example, protein is necessary for formation of red blood cells, however, consumption only averaged around 60% of recommended values in the current study. Insufficient protein intake not only inhibits the production and function of important cellular components, when energy consumption is low, protein is used to help meet energy needs instead. Moreover, dietary iron was only 20% of the recommended value in current subjects and iron is indispensable to the formation of Hb, among other things. While vitamin C is necessary to increase iron absorption from non animal-based food sources, its consumption was only around 60% of the recommended value.

Ferric iron is found in most vegetables, while ferrous iron is found in animal-based food sources. Ferric forms are reduced to ferrous forms by gastric juices and are more easily absorbed by intestinal mucosal cells; vitamin C also helps the reduction process. The IFA tablets contain ferrous iron, thereby increasing its absorption[16]. On the other hand, the composition of diets among pregnant women in the current study included more ferric than ferrous forms of iron.

Hemoglobin is the protein that enables red blood cells to carry oxygen. In its tetrameric form, Hb binds up to four irons[17]. Iron metabolism is unique given the small exchange of iron in the body each day. In fact, only 1 mg of iron needs to be absorbed by the body to maintain balance. Other needs are met from a turnover of around 35-40 mg day^{-1} [16]. However, the iron requirement during pregnancy is greater, except in the first trimester. During the first trimester, less iron is needed relative to women who are not pregnant because the mother does not menstruate and pregnancy needs are not high. In the second and third trimesters, production of red blood cells increases due to the increased need for oxygen by the fetus. The mean increase in Hb levels in the current study increased with pregnancy stage. In the first trimester, pregnant women experienced a mean increase in Hb levels of 0.09 and 0.37 g dL^{-1} in the second trimester and 1.30 g dL^{-1} in the third trimester. This is consistent with the theory that iron absorption increases dramatically in the third trimester, sometimes by more than 50%[16].

The most significant increase in Hb levels was 0.5 g dL^{-1} in the weekly group and 0.6 g dL^{-1} in the daily group and the scale of Hb change was similar in both groups. This means that weekly and daily IFA supplementation provide the same Hb-increasing effect in pregnant women with anemia. The results are likely due to the consumption of vitamin C being slightly higher in the weekly group (once a week) versus the daily group, which would increase absorption of iron from vegetable-based food sources. Although, the percentage of anemic pregnant women by the end of the study was not significantly different between the two groups, this percentage was lower in the daily (61.7%) versus the weekly (68.1%) IFA treatment group. The relatively short supplementation period (8 weeks) was likely one reason why anemia was not alleviated in all pregnant women in the current study by the end of the treatment period.

Although the Hb concentration increased with gestational age, the iron status of subjects was not known because a ferritin assessment was not completed. In addition, the absorption rate between daily (3600 mg ferrous sulfate) and weekly (480 mg ferrous sulfate) treatment over the 8 weeks study period was not investigated. Theoretically, if Hb levels are already in the anemic range, ferritin levels should also be quite low since anemia is the last phase in the process of reduction of iron in the body[18].

Another study conducted in Indonesia among pregnant women given daily and weekly doses of IFA showed a similar increase in Hb levels in both treatment groups but the increase in ferritin was higher with daily treatment[19]. Research conducted on preschool children given half the adult dose of IFA daily or twice weekly reported that both groups showed a similar increase in Hb[12]. Another study conducted in China stated that supplementation with IFA daily was quite safe and effective for preschoolers[20]. Furthermore, intermittent IFA supplementation also showed the same efficiency as daily administration in both animals and humans[13, 21-27].

The above results can be explained by the fact that IFA given too frequently will progressively reduce the absorption of iron as the intestinal mucosal cells reach saturation, while less frequent administration will make the body "iron hungry," increasing iron absorption and making it more effective[21,22,28].

The pattern of iron consumption of pregnant women herein tended to be more vegetable-based and consumption of less animal-based food sources may also help to boost the effectiveness of iron absorption. If the current research was carried out in Western countries which consume higher amounts of animal-based food sources, the results would likely differ and not be as effective. Weekly supplementation from a government program perspective is more beneficial as it saves money, produces fewer side effects and reduces interactions with iron inhibitors, such as zinc and calcium[29].

Since anemia diagnoses based on clinical symptoms do not show consistent Hb levels, clinical symptoms alone cannot be used as standard diagnostic criteria. After the 8 weeks supplementation period, a significant reduction in clinical symptoms and subjective complaints was observed in both treatment groups, indicating short-term IFA treatment can effectively improve these indices of anemia among pregnant women. With proper counseling on good IFA supplementation practices (e.g., before going to sleep at night), side effects, such as nausea and vomiting, dizziness, weakness and numbness, that are common in pregnant women were significantly reduced.

CONCLUSION

Daily and weekly short-term IFA supplementation accompanied by monitored consumption effectively improved HB levels in pregnant women with mild anemia. However, an extended interventional period will likely give different results. The IFA supplementation herein also improved clinical symptoms and subjective complaints associated with anemia. Weekly IFA supplementation should be considered for pregnant women with mild anemia in areas with a limited supply of IFA tablets. Further research is needed to determine the change in transferrin saturation and ferritin in order to obtain a more accurate iron status, as well as to examine the efficacy of interventional frequency, different dietary nutrient composition and longer supplementation periods.

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