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9 Pages

FILE SIZE

103.3KB

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World Journal of Medical Sciences 8 (3): 177-185, 2013
ISSN 1817-3055

DOI: 10.5829/idosi.wjms.2013.8.3.1115

The Influence of Multiple Micronutrient Supplementations on Hemoglobin and Serum Ferritin Levels of Pregnant Women

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Abstract: Maternal anemia remains a public health problem in Indonesia. The purpose of this study is to compare the effect of multiple micronutrient and iron folic acid supplementation on hemoglobin and ferritin serum levels of pregnant women who suffer from anemia. The study was a randomized controlled trial conducted in Maros Regency South Sulawesi Indonesia from June to December 2012. The subjects were 70 pregnant women with anemia were randomly allocated into two equal groups. The first group (n=35) received a multiple micronutrient supplement daily, second group (n=35) received a iron folic acid tablet daily, respectively for 12 consecutive weeks. Hemoglobin and ferritin serum were measured before and after the supplementation. Independent T and Paired T tests were used as appropriated. Mean hemoglobin levels increased significantly after the supplementation of multiple micronutrient (0.92±1.18 g/dl; p=0.000) whereas iron folic acid supplement did not increase significantly (0.39±1.17 g/dl; p=0.099), ferritin serum levels of the two groups were not significantly decreased after supplementation multiple micronutrient (8.18±29.77ng/ml; p=0.130) and iron folic acid (10.52±26.48 ng/ml; p=0.058). It can be concluded that multiple micronutrient is better than iron folic acid supplement to improved hemoglobin levels, but it has not been able to improve maternal iron stores. Thus, pregnant women who use iron folic acid supplements could not affectively overcome the anemia problems. Further research is needed to increase the duration of the intervention multiple micronutrient supplements, including multiple micronutrient supplementation from pre-conception through pregnancy, with a larger number of sample.

Key words: Multiple Micronutrient % Hemoglobin % Serum Ferritin % Pregnant Women

INTRODUCTION

In Indonesia, the nutritional status of pregnant women is still considered a public health problem. Data of basic health research showed that the prevalence of maternal anemia of 24.5% [1], is a public health problem was categorized according to WHO criteria (20-39.9%) [2]. This figure has decreased compared to the previous anemic data at 40.1% based on Household Health Survey, 2001.Several studies have confirmed the result of iron deficiency anemia in pregnant women include fetus growth disorder [3], the risk of preterm birth and low birth weight (LBW) by 2-3 times [4, 5]. Children born LBW will lead children to become short in childhood and adulthood, as well as the risk for the chronical disease [6] and a significant decrease in the ponderal index [7]. Incidence of LBW was associated with the incidence of some diseases in adulthood, such as hypertension,

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heart disease, glucose intolerance, insulin resistance, type 2 diabetes, hyperlipidemia, hipercolesterolemia, obesity, lung disorders and system reproduction [8].

Iron deficiency is the main cause of anemia in countries with anemia prevalence >20% [9-11]. Giving iron-folic acid supplements during this time is not the problem solving of anemia yet. Some of the factors that led to the lack of effective iron and folic acid supplementation program include: the insufficient distribution of iron tablets, the side effects of iron tablets, low compliance and lack of knowledge of pregnant women about the reasons of iron supplementation [12,13]. Multiple micronutrients were especially functional as hemopoietic to process eritropoiesis and support in the iron metabolism in the body is also an issue of nutrition in pregnant women in developing countries. Therefore, the provision of multiple micronutrient supplements replaces the iron-folic acid supplements in the health and nutrition intervention package given to pregnant women is expected to improve birth weight, growth and children's development [14].

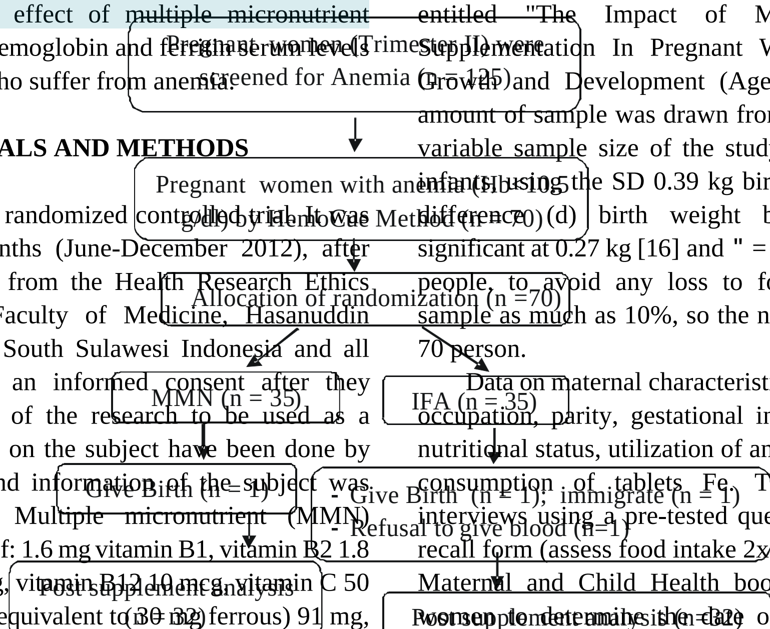
Various studies have shown that administration of multiple micronutrients supplement in pregnant women in many countries of the world have not consistent results to the improvement of maternal hematologic of pregnancy status [15]. Therefore, a study of the provision of multiple micronutrients in pregnant women is required, as the effort to reduce the prevalence of anemia in pregnant women. The objective of this study was to compare the effect of multiple micronutrient supplementations on hemoglobin and ferritin serum levels of pregnant women who suffer from anemia.

MATERIALS AND METHODS

This study was a randomized controlled trial. It was held for seventh months (June-December 2012), after obtaining permission from the Health Research Ethics Committee of the Faculty of Medicine, Hasanuddin University Makassar South Sulawesi Indonesia and all respondents signed an informed consent after they obtain explanation of the research to be used as a sample. All treatment on the subject have been done by *lege artist* method and information of the subject was kept confidentiality. Multiple micronutrient (MMN) supplements consists of: 1.6 mg vitamin B1, vitamin B2 1.8 mg, vitamin B6 2.2 mg, vitamin B12 10 mcg, vitamin C 50 mg, ferrous fumarate (equivalent to 30 mg ferrous) 91 mg, copper 0.2 mg, manganese 0.2 mg, folic acid 400 mcg. It was produced by PT. Tempo Scan Pacific Tbk Indonesia (trade name is Vitonal F), while the control group received supplements of iron folic acid (IFA) in the form of tablets containing ferrous sulfate 200 mg (equivalent to 60 mg elemental Fe) and folic acid (250 mcg) as a tablet program from Indonesian government. Micronutrient supplements given by researchers to the volunteers as much as 90 seeds per sample, while the distributor of such supplements to pregnant mothers are given once every 2 days by volunteers and supplements directly monitored by volunteers. Supervision of the implementation of micronutrient supplementation was conducted by field officers and researchers every week. Both groups was taking supplements for 3 months (90 days). Every pregnant woman consumed 1 seed micronutrient supplements every day.

The population was all pregnant women with a gestational age of 20-24 weeks. They were found in five sub-districts in Maros district, South Sulawesi province, namely sub-district Lau, sub-district Mandai, sub-district Maros Baru, sub-district Marusu and sub-district Turikale. It conducted from June to December 2012. Samples were pregnant women with anemia (hemoglobin <10.5 g/dl). inclusion criteria was gestational age 20-24 weeks (based on length menstruation period), maternal age 18-45 years, parity 0-4, singleton pregnancy, the fetus was alive, did not suffer from a chronic illness, not having hypertension, pre-eclampsia. The drop out criteria was the lysis blood samples and the pregnant women who moved from research sites. Because this study is part of a study entitled "The Impact of Multiple Micronutrient Supplementation In Pregnant Women Against Infant Growth and Development (Age 0-6 Months)" so the amount of sample was drawn from the calculation of the variable sample size of the study was the birth weight infants using the SD 0.39 kg birth weight, with a mean difference (d) birth weight babies are considered significant at 0.27 kg [16] and " = 0.05 and $ = 0.20 as 64 people, to avoid any loss to follow-up added to the sample as much as 10%, so the number of samples to be 70 person.

Data on maternal characteristics were age, education, occupation, parity, gestational interval, nutrient intake, nutritional status, utilization of antenatal care (ANC), the consumption of tablets Fe. They obtained through interviews using a pre-tested questionnaire and 24-hour recall form (assess food intake 2x24 hours) and check the Maternal and Child Health book (MCH) of pregnant women to determine the date of LMP (late menstrual period) and gestational age of pregnancy. Levels of hemoglobin (Hb) measured by *lege artist* through taking



blood at the periphery of the ring or middle finger about 10 mL and reading results performed on the machine Photometer HemoCue blood, while the vena mediana cubiti sampling as much as 3 cc using vacutainer without anticoagulant for measure the levels of maternal ferritin serum by immuno chemiluminescence method which were analyzed in the laboratory Prodia Central Jakarta, Indonesia. Before and after the end of the intervention was measured maternal hemoglobin and serum ferritin to assess the changes after receiving the supplementation. The nutritional status of pregnant women was obtained by measuring body weight using digital scales brand AND, the level of accuracy 0.1 kg, body height was measured using microtoice with 0.1 cm accuracy level and size upper arm circumference (UAC) was measured by tape meter with accuracy of 0.1 cm at the level of early intervention. Data of food intake processed by using W-Food 2I program to know the nutritional content of each food consumed by pregnant women before and after the intervention. All data were analyzed using statistical package for social science (SPSS) for windows. Paired T test was used to assess differences in the levels of hemoglobin and ferritin serum of the pregnant women before and after the intervention in both groups, whereas the difference of hemoglobin and ferritin serum in both intervention groups was analyzed using independent T test.

RESULTS

Of the 70 people were chosen to be the sample of the study, 57 people who had a complete hematologic size was 32 people in the group of multiple micronutrients (MMN) and 25 for the iron + folic acid (IFA) (Figure 1). Based on the characteristics of maternal education, nearly three-quarters of the total sample was still relatively low level of education. It was below the junior high graduation (71.4%) in the group of women who obtain multiple micronutrient supplements (MMN) and IFA supplementation group (73.4%) and was not different significantly ($p = 0.31$). Similarly, husband education and percentage of low education, was also higher in the IFA (68.6%) than the group MMN although the difference was not statistically significant. From the aspect of the job, working mother to earn an income, higher in the group of pregnant women who gain supplement MMN (31.4%) compared to IFA supplement group. While the husband's work in the majority MMN worked as a day laborer, but the IFA group there are 2 types of work husband pregnant women who were dominant were day laborers and self-employed, both of group did not different significantly. The mean family income pregnant women per month in both intervention groups also did not different significantly ($p=0.62$) which was in the range of 1.1 -1.2 million more per month (Table 1).

Fig. 1: Selection process for the study participant and reason for loss to follow-up

Table 1: Socioeconomic characteristics of pregnant women

Variable	MMN Group	IFA Group	P Value##
Family size#	5.2±2.4	4.7±1.9	0.33*
Mother's education [n (%)]			
C None	1 (2.9)	2 (5.7)	
C Unfinished primary school	6 (17.1)	10 (28.6)	
C Completed elementary school	10 (28.6)	7 (20.0)	
C Completed secondary school	8 (22.9)	7 (20.0)	
C High school graduate	7 (20.0)	9 (25.7)	
C Diploma/Graduate	3 (8.6)	0	0.31
Mother's Occupation [n (%)]			
C Trader/Sealer	2 (5.7)	2 (5.7)	
C Labor	0	1(2.9)	
C Civil servants	1 (2.9)	0	
C Work in private	1 (2.9)	1 (2.9)	
C Entrepreneurs	2 (5.7)	1 (2.9)	
C Housewife	24 (68.6)	28 (80)	
C Others	5 (14.3)	2 (5.7)	0.63
Family Income (rupiah) #	1.212.857 ±1.040.598	1.112.857 ±606.643	0.62*
Ethnicity [n (%)]			
C Bugis	16 (45.7)	16 (45.7)	
C Makassar	16 (45.7)	17 (48.6)	
C Others (Toraja and Mandar)	3 (8.6)	2 (5.7)	0.90

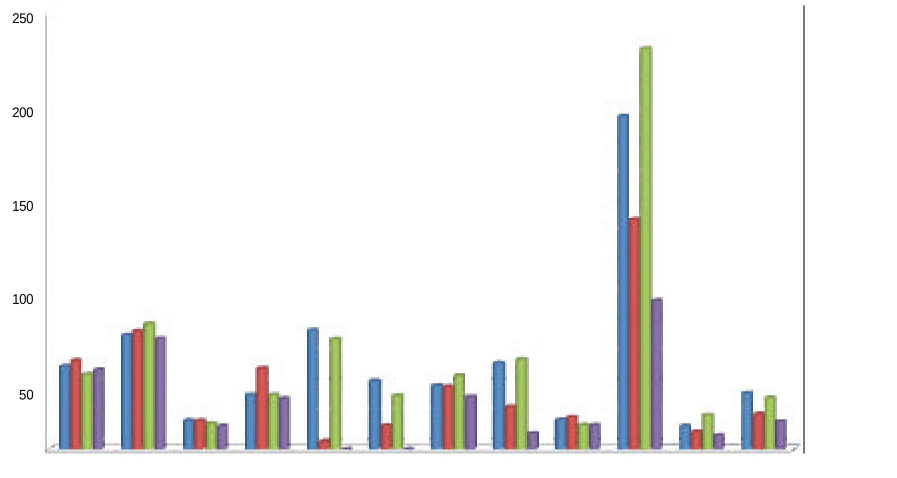
= mean ± SD; ## = U Mann Whitney Test; * = T independent Test

Table 2: Maternal characteristics

Variable	MMN Group (mean±SD)	IFA Group (mean±SD)	P value*
Maternal age (y)	27.57±6.76	26.06±6.24	0.33
Parity	1.29±1.52	0.89±0.99	0.20
Abortion	0.14±0.35	0.26±0.50	0.28
spacing pregnancies (mo)	26.31±30.09	45.63±72.57	0.15
Gestational age (wk)	21.86±1.53	22.11±1.62	0.49
Body weight (kg)	53.64±8.01	55.88±9.02	0.28
Body height (cm)	151.72±4.50	151.99±6.41	0.84

The mean maternal age was relatively similar of both intervention groups were selected as the average age of mothers in the intervention group (MMN) of 27.6 years, while the control group (IFA) ranged from 26.1 years but they were not different significantly (p=0.05). Based on the biomedical aspects of pregnant women comprising parity and abortion appeared similar in both intervention groups (p=0.05), where the average pregnant woman had a gravida 2, while the average labor history (parity) also did not different significantly (p=0.05) in both treatment groups, respectively had ever given birth to as many as one-time, even abortion almost never occurred in both intervention groups. Among the 70 pregnant women who meet the criteria of the sample (20-24 weeks gestation), most pregnant women were at an age of 20 weeks (28.6%), followed by 24 weeks (25.7%), 22 weeks (18.6 %), 23 weeks (15.7%), last 21 weeks (11.4%), with an average of gestational age did not different significantly in both the intervention group is 22 weeks (p=0.49). Similarly, a measure of weight and height of pregnant women before the intervention did not different significantly (p = 0.05) in both the intervention group, the mean body weight in group MMN (53.64 kg) and the IFA (55.88 kg), while the average body height in both treatment groups was 151.8 cm (group MMN) and 151.9 cm (IFA group) (Table 2).

The mean number of supplements consumed by pregnant women at MMN group (± 64 seeds) were higher compared to the IFA group (57 seeds), but they did not different significantly (p=0.179). The rate of compliance from MMN group and IFA group were very low (<80%). The rate of compliance from MMN group were higher (40%) than IFA (29.4%), but not different significantly (p=0.359). The low rate of compliance in both groups caused by side effects that they feel that the IFA group (26.5%) while MMN group (22.8%). The side effects were feeling of nausea/ vomiting, stomach ulcers and black stool. Based from Figure 2, the percentage of nutrient intake by pregnant women nutritional adequacy rate in



	Energy (kcal)	P[illegible]in	Vitamin E (mg)	Vitamin C (mg)	Thiamin (mg)	Riboflavin (mg)	Niacin (mg)	Pyridoxine (mg)	Folic acid (mcg)	Cyanocobalamin (mcg)	Fe (mg)	Zn (mg)
MMN before	47.58	65.42	16.47	31.33	68.46	39.29	36.67	49.41	17.1	191.92	13.37	32.15
MMN after	50.96	67.82	16.4	46.28	4.61	13.57	36.2	24.11	18.61	132.3	9.84	20.31
IFA before	42.77	72.25	14.77	31.29	63.08	30.71	42.11	51.76	13.9	230.38	19.77	29.48
IFA setelah	45.5	63.5	13.2	29.1	0	0	30.2	8.82	13.9	85.5	7.69	15.91

Fig. 2: Percentage of nutrient intake of pregnant women based on recommended dietary intakes before and after intervention at two intervention groups

Table 3: Hematologic status changes on both intervention groups

Variable	MMN Group (mean±SD)	IFA Group (mean±SD)	P value*
Hb level (g/dl) (Baseline)	10.12±0.70 [n=35]	10.05±0.90 [n=35]	0.75
Hb level (g/dl) (Endline)	11.03±1.18 [n = 32]	10.59±1.30 [n =26]	0.17
P Value (Paired t test)	0.000	0.099	
Ferritin Serum (ng/mL) (Baseline)	28.70±28.84 [n=35]	26.60±25.63 [n=35]	0.75
Feritin Serum (ng/mL) (Endline)	20.91±11.56 [n = 32]	20.36±15.69 [n=25]	0.88
P Value (Paired t test)	0.130	0.058	

the third trimester appeared that the macronutrient intake (energy and protein) in both the intervention group showed none of the macronutrients consumed by pregnant women who reach the standard of recommended dietary intake (RDA) (=77%), when compared with pregnant women in MMN and IFA groups, group MMN higher achievement of percentage of RDA macro nutrient intake compared to the IFA. Micronutrient intake in a group MMN that meets the standards of achievement of RDA (= 77%) was only vitamins A and B12, whereas none of the IFA group who meet the RDA. All micronutrient intakes of pregnant women was higher achievement of recommended dietary intake (RDA) in the MMN group than the IFA group.

Hemoglobin levels did not different between the groups obtained MMN and IFA supplements, before and after the intervention (p=0.05). However, the MMN group, hemoglobin increased by 0.91 g/dl significantly (p=0.000) after obtaining MMN supplement for 90 days, while in the IFA group increased by 0.54 g/dl, but not a statistically significant (p=0.099). After 90 days of the intervention there was the decreased of the prevalence of anemia (Hb<11 g/dl) in both the intervention group 56.3% respectively (MMN group) and 30.8% (IFA group). Ferritin Serum levels did not different in the group that gained MMN and IFA supplements, before and after the intervention (p = 0.05). In the two intervention groups, all pregnant women had the decreased levels of ferritin serum after obtaining micronutrient interventions is 7.79 ng/mL (MMN group) and 6.24 ng/mL (IFA group) (Table 3). Before intervention, the prevalence of iron deficiency (serum ferritin <15 ng/mL) in the MMN group was (28.6%) and after the intervention increased to (37.5%). At the IFA group, before the intervention there were iron deficient (40%), after the intervention there was an increase to 52%.

DISCUSSION

The results of this study showed that micronutrient intervention in both intervention groups showed an improvement or increase in hemoglobin levels, even though they did not different significantly in both groups (MMN and IFA). This can be caused by the compliance supplement consumption by pregnant women is very low (<50%), duration of intervention was quite short (only 3 months) who could not give a big leverage to the improvement hemoglobin levels significantly. These results were supported by a systematic review of studies using randomized controlled trials design by Haider *et al*., (2011) [17] that the multi-micronutrient supplementation did not provide a significant benefit to anemic mothers in the third trimester of pregnancy (RR = 1, 03, 95% CI: 0.87 to 1.22], as well as a study by Bhutta *et al*. (2009) [18] and Allen and Peerson joint study group micronutrient supplementation during pregnancy (2009a) [13] that there was no difference in the levels of hemoglobin and iron status of pregnant women who obtain multiple micronutrient supplementation with iron + folic acid supplement. Although not exhibited significantly Hemoglobin difference between the two intervention groups, but elevated levels of hemoglobin was higher in the intervention group gained MMN (0.91 g/dl) were significantly (p = 0.000) than the group that gained IFA (0.54 g/dl), the difference in both of 0.44 g/dl. It is supported by a study conducted in China that there was an increase in the concentration of hemoglobin in the multi-micronutrient group (6.9 g/l, 4.1 to 9.6 g/l, P <0.001 higher than in the IFA (5.0 g/l, 2.0 to 8.0 g/l, P = 0.001) [19].

This, similar with the statement Stoltzfus *et al*., [20] that in order to estimate the distribution of hemoglobin when iron deficiency was corrected, the average of the world showed an increase in hemoglobin concentration of approximately 0.45 g/dl (range: 0.1-1.28 g/dl). Studies in developed countries showed lower hemoglobin response in those who had higher initial hemoglobin, mean change 1.13 g/dl in mean hemoglobin (Hb) initial <10.0 g/dl compared to 0.85 g/dl with Hemoglobin level 11.0 to 11.9 g/dl.The prevalence of anemia in the MMN group after gaining over 90 days supplementation, decreased by 56.3% which was higher than in the IFA only 30.8%. The same was found by Osrin (2005) [21] that the decrease in the prevalence of anemia was higher in the group that gained MMN supplementation than the IFA, as well as studies conducted by Zeng *et al*., (2008) [19] that there were more than 40% of pregnant women are anemic in the third trimester. It proves that not only the nutritional anemia caused by iron deficiency and folic acid, but also because of other micronutrient deficiencies that also contributes to the metabolism of iron in the body, as described by Zimmerman (2007) [22] that nutritional anemia, other than caused by iron deficiency may also be caused by a deficiency of various micronutrients that contributes to the metabolism of iron in the body, such as Vitamin A, Vitamin C, B12, folic acid, zinc, copper and protein (amino acid deficiency inhibits the process of erythropoiesis through interference erythropoietin in hypoxic conditions). Vitamin A [9, 23, 24], vitamin B12 [24,25], vitamin B2 [26, 27], vitamin C [27, 28], selenium [29], contributing to nutritional anemia, through the role as precursor of erythrocytes formation in the bone marrow, hemoglobin formation, metabolism, absorption and mobilization of iron in body [12, 30].

Increased hemoglobin levels and decrease the prevalence of anemia was higher in the group of pregnant women who gained MMN supplements than the IFA. This can be explained by taking supplements adherence, that pregnant women who had normal hemoglobin status (= 11 g / dl) supplements compliance rate was higher in group MMN (72.7%) compared to the IFA (27.3%). This is because the side effects they felt by the IFA group was higher (26.5%) than MMN group (22.8%). According to Harrison (2010) [31] that supplementation with iron and folic acid in pregnant women did not give more results on maternal hematologic improvement because of poor adherence due to side effects of the supplement. The results of the pooled analysis of studies using multiple micronutrient supplementation conducted by Allen *et al*., (2009a) [13] indicated that multiple micronutrient supplements improve hemoglobin synthesis, on the same level with iron supplementation with or without folic acid, although often contain iron which lower. Supplementation with different types of micronutrients may be a necessity for the pregnant mother [6] recommended replacing IFA supplements.With respect to the persistence of pregnant women with anemia in this study, as well as the amount of consumption of supplements given still less (low compliance) due to side effects that occur because of the high doses of iron in supplements IFA, also may be caused by the delay in the start of supplementation women who may be given from preconception continued through pregnancy to maintain sufficient iron levels during pregnancy [17].

The results of this study showed that micronutrient interventions in both treatment groups could not improve the iron deposits (mean ferritin serum) in the third trimester pregnant woman's body, even a decline in ferritin serum levels in the two intervention groups, namely 7.79 ng/mL (MMN group) and 6.24 ng/mL (IFA group), although the decrease was not significantly ($p = 0.05$). It can be explained that the decline in maternal ferritin serum may be due to an increased need for iron as the pregnancy progresses to meet the needs of the mother and to be transferred to the fetus, although had received micronutrient supplements, but only able to improve hemoglobin levels. High enough reserves owned by pregnant women in the second trimester, was used with supplement and food intake to form hemoglobin, in order to improve hemoglobin status of anemic pregnant women in the early onset of supplementation and less to be stored as a backup pregnant. This was consistent with that expressed by Asif *et al* 2007) [32] that ferritin serum decreased progressively at 32 weeks' gestation to 50% of the levels before pregnancy, this was caused by hemodilution and iron mobilization. Although ferritin levels likely influenced by dilution of plasma at a late stage of pregnancy, concentrations <15 μg/l showed iron depletion at all stages of pregnancy.

The results of this study are also supported by the statement (Kaufer, *et al*., 1990) [33] that ferritin serum is usually decreased with increasing gestational age, one of which was used to transfer to the fetus at gestational age >30 weeks [34] and fetal iron stores in the third trimester, until the baby borned [35]. Therefore, to meet the needs of maternal iron, a woman should have a reserve >300 mg at the time of entering the pregnancy [36]. The need for iron increases in the third trimester of pregnancy, resulting in higher iron requirements for pregnancy is about 840 mg. In addition, other opinions from experts cited by Raza (2011) [36] that the reduced levels of ferritin serum as a possible result of the use for the mass expansion of the red blood cells of pregnant women. Because there was the decreased of ferritin serum levels in the study, resulting in the prevalence of iron deficiency (ferritin serum <15 ng/mL) had an increase of 8.9% in the MMN group and 12% in the IFA were higher than the MMN.

Studies in East London also showed the same results from this study, that women who obtained multiple micronutrient supplementation also decreased in ferritin serum in the third trimester (34 weeks gestation), from 46.5 mg/l to 16 mg/l or decreased by 30.5 mg/l and the prevalence of iron deficiency (ferritin serum <15 ug/l) increased from 10% to 44% (an increase of 34%) [37]. Decrease in mean ferritin serum levels and an increase in the prevalence of iron deficiency after receiving multiple micronutrient supplements such, higher than the results of this study. In conclusion, the supplementation of MMN is better than IFA in improving hemoglobin levels, but they have not been able to improve maternal iron stores. So that, pregnant women who use IFA supplements are not effectively to overcome the anemia problem. Further research is needed to increase the duration of the intervention multiple micronutrient supplements, including multiple micronutrient supplementation from pre-conception through pregnancy, with a larger number of sample.

ACKNOWLEDGEMENTS

Gratitude to all parties who contributed directly or indirectly in this study, including: (1) Directorate of Higher Education, Ministry of Education and Culture of the Republic of Indonesia, (2) PT. Tempo Scan Pacific Tbk, (3) Pregnant women who were respondents in this study, without their active participation, this research would not be possible to complete, (4) the midwife who helped birth mothers who also contributed much to finish this study.

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