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EFFECT OF MULTI MICRONUTRIENT SUPPLEMENTATION ON HEMOGLOBIN LEVELS IN PREGNANT WOMEN WITH ANEMIA

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Abstract
Background: The coverage of 90 Fe tablets in Semarang in 2015 was 26.619 of 29.490 pregnant women (97%) but the incidence of anemia in pregnant women was still quite high. One important factor which influences the levels of hemoglobin is multi micronutrient.
Objective: This study aims to analyze the changes in hemoglobin levels with multi micronutrient supplementation in pregnant women with anemia.
Methods: A quasi-experimental study with randomized control group pre-posttest design. The study samples were 40 pregnant women with gestational age of 20 ± 1 weeks divided into two groups, the intervention group (multi micronutrient supplementation) and the control group (Fe supplementation) for six weeks. The study was conducted from November 2016 to January 2017. The levels of hemoglobin were measured using cyanmethemoglobin. Paired t test and independent t test were used for data analyses.
Results: The average of the increase in hemoglobin levels after multi micronutrient supplementation was 1.545 (1.292) g/dl, whereas the average of the increase in hemoglobin levels after Fe supplementation was 0.757 (0.742) g/dl. The difference in hemoglobin levels before and after multi micronutrient supplementation was significantly different (p=0.049). Cohen's d effect size test showed value of 0.748.
Conclusion: Multi micronutrient supplementation could improve hemoglobin levels. The increase in the levels of hemoglobin with multi micronutrient supplementation was higher than Fe supplementation.

Keywords: multi micronutrient; Fe; pregnant women with anemia

INTRODUCTION

Anemia remains one of the health problems experienced by most countries in the world, especially in developing countries. Globally in 2011, according to WHO, anemia was suffered by 29% of non-pregnant women and 38% of pregnant women aged 15-49 years (World Health, 2014). According to World Data Bank in 2011 pregnant women who were anemic in Myanmar was 33.3%, Philippines was 32.3%, Thailand was 30%, Indonesia was 29.6%, Singapore was 28.5%, Brunei Darussalam was 28.0%, Malaysia was 26.6%, and Vietnam was 23.5% (bank, 2016).

The prevalence of anemia in Indonesia is still relatively high. Based on Basic Health Research (Riskesdas), most of pregnant women had hypochromic anemia caused by iron deficiency as much as 59%. While macrocytic anemia caused by vitamin B12

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deficiency as much as 10.3% (Departemen Kesehatan, 2008). Based on Riskesdas in 2013, the prevalence of anemia in Indonesian population reached 21.7%. The groups at risk of anemia with the greatest prevalence were among pregnant women of 31.7%, age 5-12 years of 29%, under five children of 28.1%, young women aged 13-18 years of 22.7%, as well as women aged age 15-49 of 22.7% (MOH, 2013). The coverage of pregnant women who received Fe tablet in Central Java Province in 2012 was 90.74% (Dinkes, 2014).

During pregnancy the main factor, which causes nutritional anemia, is lack of nutrition, especially iron in the daily diet. Less iron intake and low absorption of iron due to other micronutrient deficiencies affect a decrease in blood hemoglobin levels and cause anemia.[5] the prevalence of anemia during pregnancy is risky for the mother and baby. Risks that can occur in the form of complications during pregnancy and childbirth and cause mortality, low birth weight, and growth/early development retardation (Ramakrishnan, 2000).

One of the government's efforts to overcome anemia is the provision of the iron tablet for pregnant women, teenagers and Women of Fertile Age (WUS) groups. Treatment of anemia in pregnancy has been focused on iron. Besides iron, red cell formation process requires the other micronutrient substances, which are necessary as a precursor to the process of erythropoiesis in the spinal cord. The presence of micronutrients such as vitamin A, vitamin B, vitamin C, Zinc, Folic acid also plays an important role in helping to improve the absorption of iron in the body. Deficiency of micronutrients such as vitamin A, iron, iodine and folic acid is very common during pregnancy because of the increased nutritional needs of the mother and the fetus development (WHO, 2015). Multi micronutrients are naturally found in many fruits and vegetables. But the total diet study results showed a mean of vegetable and dairy consumption per person per day in Indonesian population by age group was only 57.1%. The mean of fruit consumption in Indonesia was still low at only 33.5 grams per person per day (Balitbangkes, 2014).

Based on the results of a study showed that there was a correlation between the intake of folic acid, vitamin B 12, vitamin E, and Cu and the levels hemoglobin (Besuni, Jafar, & Indriasari, 2013). The analysis results in adolescents showed that there was a relationship between nutritional deficiency and anemia. Adolescents with folic acid daily intake of <150 g/day had 2.8 times risk of suffering from anemia. Adolescents with vitamin C intake of <60 mg/day had 1.13 times risk of suffering from anemia (Tampubolon & Hadi, 2005).

Studies on micronutrients showed that vitamins and minerals had a correlation with hemoglobin levels. Study results conducted in pregnant women in South Sulawesi showed that hemoglobin levels were associated with nutritional status, iron tablet intake and consumption patterns. The results showed that the prevalence of anemia among pregnant women reached 41%. Based on this study it was found that the mean of vitamin consumption in pregnant women was only about 40% of the Nutrient Adequacy Score (NAS) (Fatimah, Hadju, Bahar, & Abdullah, 2011).

Results of a study on children in India showed that there was a significant increase in the group with micronutrient supplements and biochemical parameters on the status of iron and vitamin A. Hemoglobin increased by 0.52 g/dL, retinol by 8.56 mg/dL, ferritin by 108 mg/L, iron of 1.27 mg and the prevalence decrease of retinol deficiency was from 51.6% to 28.1%, anemia from 46.0% to 32.6%, iron deficiency from 66.9% to 51.3 % and iron deficiency anemia from 35.2% to 31.0%, while the prevalence in the other two control groups showed no significant differences (Kumar, Nirmalan, Erhardt, Rahmathullah, & Rajagopalan, 2014). A meta-analysis study concluded that micronutrient supplementation in pregnant women was more effective than iron and folic acid supplementation in reducing the risk of low birth weight and premature birth (Kawai, Spiegelman, Shankar, & Fawzi, 2011).

Based on data from Semarang Health Office in 2015, the incidences of maternal anemia were 3.861 of 21.057 pregnant women

(18.34%). The coverage of 90 tablets Fe in Semarang in 2015 was 26.619 of 29.490 pregnant women (97%). Data form 37 Public Health Centers in Semarang showed that the highest incidence of anemia in 2015 was in Bangetayu PHC as many as 337 of 1.282 pregnant women (26.29%). Data in 2014 showed that anemia among pregnant women in the PHC work area were also high as many as 311 of 754 pregnant women (41.25%) (Dinkes, 2014).

Efforts have been made by Semarang Health Office, among others, the provision of 90 Fe tablets for pregnant women during pregnancy (Dinkes, 2014). Other efforts by healthcare workers is by providing counseling on nutrition that could help increase the levels of hemoglobin and proper Fe consumption. Monitoring and motivation were also given by health surveillance officers (Gasurkes) of health cadres in the community. While multi micronutrient supplementation has not been done.

METHODS

Research Design

This was a quasi-experimental study with randomized control group pre-posttest design.

Setting

The study was conducted on November 3, 2016 until January 11, 2017.

Population and Sample

The study populations were anemic pregnant women in Bangetayu PHC. For test one tail hypothesis with power 95%, significance difference in the two groups of 0.05 and 1.28 literature using the following formula (Dahlan Sopiyudin, 2009):

$$n = \frac{2\,(Z\alpha+Z\beta)^2\sigma^2}{(\mu_c-\mu_1)^2}$$

n = Number of samples per group

Zα = the value of the standard normal distribution that is equal to the significance level (for α= 0.05 is 1.64)

Z β = the value of the standard normal distribution that is equal to the significance level (for α= 0.05 is 1.28)

σ = standard deviation of outcome

μc-μ1 = the difference of mean outcome before and after intervention

$$n = \frac{2\,(Z\alpha+Z\beta)^2\sigma^2}{(\mu_c-\mu_1)^2}$$

$$n = \frac{2\,(1.64+1.28)^2(0.78)^2}{(0.65)}$$

n = 15.96 = 16 samples

To anticipate drop out, the researchers make corrections to the sample size, by adding a large number of subjects in order to be fulfilled using the sample was calculated as follows:

$$n' = \frac{n}{1-f}$$

n = sample size calculated

f = estimate of the proportion of dropouts, an estimated 20% (f = 0.2)

$$n' = \frac{n}{1-f}$$

$$n' = \frac{16}{1-0.2} = 20$$

To test one-tail hypothesis with 95% power and significance of 0.05 and using the above formula, 20 samples were obtained for each either the intervention group (multi-micronutrient supplementation) or the control group (Fe supplementation).

Samples that met the inclusion and exclusion criteria were acquired as many as 40 people. Inclusion criteria for this study were pregnant women with the gestational age of 20 ± 1 weeks and experienced anemia (hemoglobin levels of 7.0 to 10.5 g/dl). While the exclusion criteria were pregnant women suffering from kidney disease, malaria, intestinal worms based on interviews; there was a family history of the disease blood disorders such as thalassemia and sickle moon; the use of certain medications which could increase the levels of hemoglobin (chemotherapy or ARV); had a habit of drinking tea or coffee during pregnancy; and vegetarian. The drop out criteria were if the respondent died; resigned, missed from the monitoring/changes in address, and were disobedient in taking supplements of more than 10% of the number of tablets given.

The sampling technique used simple random sampling, single blind. Randomization was performed by using sealed envelopes to determine the samples in the intervention group or the control group and signed informed consent.

Intervention

Respondents in the intervention group were given multi micronutrient supplementation. Fe supplementation was given for the control group. Multi micronutrient supplementation is supplementation in tablets form, each tablet content of vitamins and minerals (vitamin A 6000 IU, vitamin D 400 IU, vitamin C 100 mg, vitamin B1 10 mg, vitamin B2 2.5 mg, vitamin B6 15 mg, vitamin B12 4 mcg, niacinamide 20 mg, Ca pantothenate 7.5 mg, folic acid 1 mg, Fe fumarate 90 mg, Ca lactate 250 mg, iodine 0.1 mg). Fe supplementation is supplementation in tablets form, each tablet content of Fe 90 mg and folic acid 0.4 mg. Supplementation was given once a day for 42 days. Respondents were reminded to consume supplement via Short Message Service (SMS) every week.

Instrument

The data in this study were primary data. Data collection instrument used cyanmetho-hemoglobin examination to measure hemoglobin levels with conducted twice, before given the intervention and 6 weeks after the intervention.

Ethical Consideration

The process of data collection was performed by doing a home visit and coming to pregnant women class on 88 pregnant women. This study has been getting ethical clearance from the Research Ethics Committee of Heath Polytechnic of Semarang (No: 212/KEPK /Poltekkes-Smg/EC/2016). Respondents in this study have given informed consent about this study and willing to participate by signing letter of informed consent.

Data Analysis

Paired t test and independent t test were used for data analysis.

RESULTS

Characteristics of the Respondents

All respondents followed the study until the end and there was no dropout. Characteristics of the respondents in this study consisted of age, parity, pregnancy spacing, nutritional status and economic status. Each variable was analyzed to see the difference between the two groups. Distribution of the respondents' characteristics is shown in Table 1.

The analysis on the respondents' characteristics obtained non-significant differences in the characteristics (age p=0.457, parity p=0.736, pregnancy spacing p=0.073, nutritional status p=0.849 and economic status p=0.723) similar in multi-micronutrient supplementation group and Fe supplementation group. So, the characteristics of the respondents had the same effect on the two groups.

Table 1 Distribution of general characteristics and health characteristics (nutritional status)

Variable	MMN Supplementation	Fe Supplementation	p-value
Age (years) (n i=20; n k=20)			
Mean (SD)	27.80(4.51)	29.05(5.91)	0.457
Median	27	31	
Minimum	21	20	
Maximum	37	38	

Parity (people) (n i=20; n k=20)			
Primigravida	6	7	0.736
Multigravida	14	13	
Pregnancy spacing (month) (n i=14; n k=13)	55.43(25.55)	71.54(29.44)	0.073
Mean (SD)	60	84	
Median	14	18	
Minimum	84	108	
Maximum			
Nutritional status (cm) (n i=20; n k=20)			
Mean (SD)	25.20(3.06)	25.03(2.78)	0.849
Median	24.75	24	
Minimum	21	21	
Maximum	33	32	
Economic status (people) (n i=20; n k=20)			
Under UMK/Standard	6	5	0.723
Above UMK/Standard	14	15	

Table 2 Hemoglobin Levels before and after supplementation

Group	MMN Supplementation	Fe Supplementation
Before intervention (gr/dl) (n i=20; n k=20)		
Mean(SD)	9.71(0.79)	10.02(0.37)
Median	10.09	9.96
Minimum	8.22	9.33
Maximum	10.50	10.50
After intervention (gr/dl) (n i=20; n k=20)		
Mean(SD)	11.26(1.32)	10.77(0.82)
Median	10.96	10.75
Minimum	9.51	9.10
Maximum	13.98	12.54
	p=0.0001	p=0.0001

Hemoglobin levels in the multi micronutrient supplementation group before supplementation showed the mean of 9.71 (0.79) g/dl and the mean after supplementation was 11.26 (1.32) g/dl. Hemoglobin levels before and after multi micronutrient supplementation showed significant difference (p=0.0001).

Hemoglobin levels in the Fe supplementation group before supplementation showed the mean of 10.02 (0.37) g/dl and after supplementation showed the mean of 10.77 (0.81) g/dl. Hemoglobin levels after multi-micronutrient supplementation was higher than before multi micronutrient supplementation. Hemoglobin levels before and after Fe supplementation had significant difference (p=0.0001). Hemoglobin levels after Fe supplementation was higher than before Fe supplementation.

Table 3 The results of difference test of the difference in hemoglobin levels before and after administration of multi micronutrient supplementation and Fe supplementation

Group	MMN Supplementation	Fe Supplementation	p-value
Difference in hemoglobin levels before and after (gr/dl) (N i=20; N k=20)			
Mean(SD)	1.545(1.292)	0.757(0.742)	0.049
Median	1.38	0.71	
Minimum	0.20	-0.60	
Maximum	5.43	2.14	

Based on the above table it can be seen that the mean increase in hemoglobin levels after multi-micronutrient supplementation was 1.545 (1.292) g/dl, while the mean increase in hemoglobin levels after Fe supplementation was 0.757 (0.742) g/dl. Difference in hemoglobin levels before and after the multi-micronutrient supplementation was significantly different (p=0.049). The increase of hemoglobin levels after multi micronutrient supplementation was higher than after Fe supplementation. Based on of Cohen's d effect size test, in this study was 0.748.

DISCUSSION

Difference in hemoglobin levels in the intervention group

Hemoglobin levels after multi micronutrient supplementation was higher than before supplementation. Hemoglobin levels in multi micronutrient supplementation group experienced a mean increase of 1.545 g/dl. The mean of hemoglobin levels in pregnant women before multi micronutrient supplementation was 9.71 g/dl, considered as moderate anemia (<10 g/dl). After the multi-micronutrient supplementation for 6 weeks, the mean of hemoglobin levels in pregnant women became 11.26 g/dl, categorized as non-anemic.

This study is in line with the results of a study conducted in China, which showed that the combination of vitamin and multi-micronutrients was more effectively to increase hemoglobin levels in preschool children compared to the provision of Vitamin alone or a combination of Vitamin A and zinc. The group that got multi micronutrients had an increase in the mean of hemoglobin levels of 0.635 g/dl (Chen et al., 2012). The factor that influences the increase in hemoglobin is the content of riboflavin, vitamin B-12 and folic acid that play a role in the metabolism of iron or hemoglobin synthesis. Vitamin A is directly as a facilitator with an impact in hematopoiesis. Vitamin A has important role in the regeneration of cells including erythrocytes (Chen et al., 2012; Grober, 2013). A study conducted on female adolescents in Bangladesh showed that the group who were given multi-micronutrient-fortified beverage had increased serum ferritin compared to the group that was not given. In addition the group with multi-micronutrient-fortified beverage also experienced an increase in weight, UAC size and BMI (Hyder et al., 2007). Results of a study conducted on pregnant women in China found that Fe supplementation with a combination of retinol and riboflavin vitamins had an increase in hematological status as well as well as oxidative stress and erythrocyte membrane fluidity. Hematologic status in the form of hemoglobin levels increased by 2.18 g/dl compared to the control group. Oxidative stress parameters was indicated by increased glutathione peroxidase activity of 87.9 IU/ml and the decrease in malondialdehyde levels by 2.56 mmol/l (Ma et al., 2010). Based on the study results, it can be concluded that multi-micronutrient supplementation in pregnant women with anemia could improve hemoglobin levels.

Difference in hemoglobin levels in the control group

Hemoglobin levels after Fe supplementation was higher than before supplementation. Hemoglobin levels in Fe supplementation group had a mean increase of 0.757 g/dl. The mean of hemoglobin levels in pregnant women before Fe supplementation was 10.02 g/dl, categorized as mild anemia (<10 g/dl). After Fe supplementation for 6 weeks, the mean of hemoglobin levels in pregnant women became 10.77 g/dl, categorized as non-anemic. The study results are consistent with the results of a study on tobacco leaf sorters women in Deli Serdang said that iron tablet (Fe) supplementation for 3 months could increase hemoglobin levels by 2.14 g/dl. The results also showed that the hemoglobin level was closely related to with work productivity (Oppusunggu, 2009). Results of a meta-analysis of three studies showed that Fe supplementation orally for 4-6 weeks might increase hemoglobin levels mean of 0.35 g/dl. Results of a study conducted in patients after surgery showed that there was an increase in hemoglobin of 2.0 g/dl after Fe therapy for 4 weeks (Tay & Soiza, 2015). The results are consistent with the results of a study in Padang, which stated that Fe tablet supplementation had a relationship with anemia status of pregnant women. Fe tablet consumption could affect the Fe adequacy of pregnant women (Azra & Rosha, 2015).

Based on these results it can be concluded that the Fe supplementation in pregnant women with anemia could improve hemoglobin levels. Fe supplementation that has become a government program was proven to increase hemoglobin levels.

Difference in hemoglobin levels in the intervention group and the control group

Based on these results an increase in hemoglobin levels in multi micronutrient supplementation group was higher than the increase in hemoglobin levels in control group. The mean of hemoglobin levels after multi micronutrient supplementation was increased by 1.545 g/dl. The mean of hemoglobin levels after Fe supplementation was increased by 0.757 g/dl.

Multi micronutrient supplementation is a necessary supplement for pregnant women, which contains vitamin A, vitamin B1, vitamin B2, vitamin B6, vitamin B12, vitamin C, folic acid, and Fe. In the process of erythrocytes maturation, the spinal cord needs many precursors so for effective erythropoiesis process. Precursors include iron, vitamin C, vitamin B1, vitamin B2, vitamin B12 and oxygen (O2) that are required by the erythropoietin hormone (Hofbrand, Petit, & Moss, 2013). Complete multi micronutrients are jointly supporting the increasing levels of hemoglobin. Vitamin A is important in iron metabolism and the production of hemoglobin. Vitamin A plays a role as a facilitator of ferritin use in hematopoietic process (Barasi, 2013). Vitamin A plays a role in increasing the use of iron in hematopoiesis. Vitamin A has a role related to erythrocytes in the production of erythrocytes; protein synthesis and iron transfer both in mobilization and incorporation. Vitamin A can directly stimulate erythropoiesis (Grober, 2013).

Other micronutrients contribute indirectly and together act as a coenzyme in the hematopoietic process. Vitamin B2 helps to increase the metabolism of folic acid, pyridoxine and niacin. Deficiency of vitamin B 2 results in lower absorption of micronutrients, especially iron so that may cause the occurrence of hypochromic anemia (Barasi, 2013). Vitamin B6 plays a role in the formation of heme precursor in hemoglobin called alpha-delta-aminolaevulinic acid synthase. In addition, pyridoxine also assists in the process of iron incorporation into heme (Grober, 2013). One major function of vitamin B12 is in cell metabolism. Vitamin B12 plays a role in the formation of red blood cells or erythrocytes in the process of cell maturation (Almatsier, 2002).

Folic acid along with vitamin B12 affects the hemoglobin levels that are required in the erythrocyte's synthesis. Folic acid plays a role in the production of heme to form purine and pyrimidine in the synthesis of DNA and RNA in the erythropoiesis process. Folic acid or vitamin B12 deficiency may cause the growing cells are not capable of performing DNA replication prior to division. So, the erythrocytes produced will have larger size (megaloblastic) with lower density and smaller amounts. So that folic acid deficiency can cause megaloblastic anemia and macrocytic anemia (Almatsier, 2002).

Vitamin C plays a role to reduce the ferry into the ferrous in the small intestine that facilitates the absorption of iron. Vitamin C can increase absorption of iron in the form of non-heme up to four times. Vitamin C plays a role in the transfer of iron from transferrin in the plasma into ferritin stored in liver (Almatsier, 2002). Another component, which plays a key role in hemoglobin, is iron. Iron plays a role in oxygen transportation and storage. Iron is a component of hemoglobin that carries oxygen throughout the body. Iron is an essential element in the formation of heme protein composed of porphyrin protoporphyrin compounds and trivalent Fe (Grober, 2013).

The study results are consistent with the results of a study suggested that between multi micronutrient supplementation compared to no multi micronutrient supplementation or placebo, there was a significant difference in reducing anemia in pregnant women. The group that received multi micronutrient supplementation compared to group that received iron and folic acid supplementation might reduce anemia in pregnant women by 1.23 times (Haider & Bhutta, 2006). Another study said that there was a significant difference in the increase in hemoglobin levels between the groups with iron and vitamin C supplementation compared to the iron supplementation group. The mean of hemoglobin levels in women of childbearing age for 12 weeks in the iron and vitamin C supplementation group of 1.937 g/dl was higher compared to the iron group of 1.547 gr/dl (Utama, Listiana, & Susanti, 2013). Another study conducted on girls in Central Java showed a greater intake of iron, zinc, copper, folic acid and vitamin B 6, the higher the hemoglobin levels. Zinc is a cofactor in the retinol oxidation reaction; thus, zinc indirectly affected the iron metabolism. Copper helps the absorption of iron, helps hematopoiesis, and stimulates the release of ferritin contained in the liver. Folic and vitamin B6 also play important role in hematopoiesis process (Cendani & Murbawani, 2011).

Results of a study on girls showed that the addition of multi-vitamins on iron supplement with a certain dose taken once a week compared to the consumption of Fe tablets and the control group (placebo) could significantly improve iron status by using receptor transferrin serum (STfR) and serum ferritin (SF) indicators (Besuni et al., 2013). Based on the study results it can be concluded that multi-micronutrient supplementation in pregnant women with anemia could improve hemoglobin higher compared to Fe supplementation.

CONCLUSION

Based on the study results, multi micronutrient supplementation and Fe supplementation could improve hemoglobin levels. An increased level of hemoglobin with multi-micronutrient supplementation was 2-fold higher than that Fe supplementation, and multi-micronutrient supplementation in pregnant women should be considered or proposed compared to only Fe supplementation in the treatment of anemia in pregnant women. Further study is needed to take into account the recall diet of the respondents, screening for diseases that affect hemoglobin levels and types of anemia by using accurate laboratory tests and a more extensive study site and longer study duration until delivery (time series).

Declaration of Conflicting Interest

None declared.

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Author Contribution

All authors contributed equally in this study.

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