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Original Article

Hemoglobin Levels of Pregnant Women Consuming Multiple Micronutrients VS Fe+Folate in Banggai District

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ABSTRACT

Providing Fe+Folate for a long time to pregnant women has not been able to show a significant reduction in the incidence of anemia during pregnancy. This study aims to determine the effect of consuming multiple micronutrient supplements on the Hb levels amonv pregnant women in Banggai District. This was a quasi-experimental study with a non-randomised community trial and pre and post-test control group design, which involved 48 pregnant women assigned in the intervention and control groups. This study was conducted in Banggai District in 2020. The intervention group involved pregnant women who were administered with Multiple Micronutrient (MMN) supplements based on the UNIMMAP formula. The control group involved pregnant women who were administered with Fe+Folate supplements. Supplements were administered during the second trimester of pregnancy. Hemoglobin levels were assessed at the 12th week and 24th week of pregnancy. Various anthropometric characteristics and measures were assessed at study baseline. Hemoglobin levels were assessed using the Hemocue Hb 201 tool. Nutritional intake was assessed using the Semi Quantitative-Food Frequency Questionnaire (SQ-FFQ). Data were analyzed using the chi-square test, independent t-test and dependent t-test. The results of the study showed that during the second trimester of pregnancy, the mean hemoglobin level in the intervention group who were given MMN decreased by 0.3 g/dl (p-Value=0.143) and in the control group who were given Fe+Folate decreased by 0.1 g/dl (p-Value=0.408). The adifference in the decrease was not statistically significant. At the 24th week of pregnancy, the mean hemoglobin level of pregnant women who were given MMN was 0.1 g/dl higher than those who were given Fe+Folate. Such difference was not statistically significant (p-Value=0.415). Further study needs to be conducted to examine the effect of MMN and Fe+Folate on hemoglobin levels based on anemia status, characteristics of pregnant women and health status.

Keywords: *Multiple Micronutrients, Hemoglobin Levels, Pregnant Women*

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INTRODUCTION

Anemia is a major nutritional problem in Indonesia, including pregnant women. Anemia is a condition in which the amount of red blood cells or the concentration of hemoglobin in them is lower than normal depending on age, gender, physiological conditions, smoking habits and altitude of residence[1]. According to Rohrig, 2016 hemoglobin is a metalloprotein containing iron which functions to transport oxygen in red blood cells throughout the body[2]. If the amount of hemoglobin is too low or abnormal, there will be a decrease in the blood's capacity to carry oxygen to body tissues. This further causes symptoms such as fatigue, weakness, dizziness and shortness of breath. The most common causes of anemia include nutritional deficiencies, especially iron deficiency or impaired iron absorption. However, deficiencies of folate, vitamin B12 and Vitamin A are also important causes of anemia[1].

Populations with greater iron requirements, such as growing children and pregnant women, are particularly at risk of anemia. Data derived from the World Health Organization (WHO) in 2019 showed that globally, the prevalence of anemia in pregnant women throughout the world was 36.5%[3]. Furthermore, based on basic health research in 2013, the prevalence of anemia in pregnant women was 37.1% and increased to 48.9% in 2018 [4]. A survey conducted by Wijianto et al in 2010 showed that the percentage of pregnant women who experienced nutritional anemia was 21.4% (3 out of 7 pregnant women), 16.1% at risk of CED and 10.7% of underweight at 10 stunting loci in Banggai District[5].

Pregnant women who experience iron deficiency anemia are associated with adverse reproductive outcomes such as premature birth, low birth weight babies, and reduced iron reserves for the baby, which can lead to impaired child development and intelligence. Failure to decrease the incidence of anemia can result in impaired health and quality of life among milions of women, and can further disrupt children's development and learning. Anemia is an indicator of poor nutrition and poor health[3]. A previous study conducted by Lalusu et al in 2018 showed that 55 of 187 teenagers studied (29%) had anemia. Teenagers with anemia were mostly had poor nutritional status by 89%, while 11% had good nutritional status[6].

The diet of most women of childbearing age in Indonesia is still relatively poor, especially in terms of vegetable and fruit consumption. Almost the entire Indonesian population aged 15 years and over does not consume sufficient vegetables and fruit. 2018 Basic Health Research (RKD) showed that the proportion of vegetable and fruit consumption of less than 5 portions per day among residents ≥15 years increased from 93.5% in 2013 to 95.5% in 2018[4]. Adolescent health survey in Luwuk City, Banggai District revealed that fruit consumption, vegetable consumption, breakfast and the habit of bringing food to school were still low among teenagers (22-66%). On the other hand, there were still teenagers who consumed fast food and carbonated drinks (20-33%)[6]. Teenagers are the forerunners of couples of childbearing age, especially teenage girls who will become pregnant mothers in the future.

Women living in developing or low-income countries are most vulnerable to malnutrition. The need for nutritious food during pregnancy has not become a priority need in the family. Therefore, when pregnant women do not have access to nutritious food, the risk of pregnancy complications and the health of the fetus and baby in the future will increase. In addition, dietary factors alone are not enough to meet the body's vitamin and mineral needs, especially micronutrient needs. Thus, the use of supplements is expected to reduce the risk of inadequate intake of various micronutrients.

Currently, the nutritional intervention is still provided in the form of iron folate supplements which are aimed at anticipating problems with anemia and fetal growth and development during pregnancy since anemia is still a crucial problem for pregnant women. The incidence of anemia from year to year does not show a significant decrease. Meanwhile, pregnant women also need other micronutrient components in the form of vitamins and minerals which are expected to prevent anemia and various health problems during pregnancy. A previous study conducted by Siregar et al. in 2020 proved that there was an effect of consuming Ambon bananas on the increase in Hb levels among pregnant women with anemia. It is known that Ambon bananas are rich in vitamins B6 and B12 which are needed in hemoglobin synthesis[7]. Therefore, iron/folate supplements to pregnant women should be added by other micronutrient supplementation. Combining these micronutrients into one supplement would be efficient. Multiple Micronutrient (MMN) supplements are one of the global strategies recommended by the United Nations International Childhood Emergency Fund (UNICEF) to prevent micronutrient deficiencies. A study conducted by Mashalina in 2012 revealed that apart from containing iron, MMN also contains 15 types of vitamins and minerals which are very important for pregnant women[8].

This study aims to determine the effect of multi-micronutrient supplements on the hemoglobin levels among pregnant women in Banggai District. The study analyzed the differences in mean hemoglobin levels at the

12th week of pregnancy and the 24th week of pregnancy between pregnant women who consumed multi-micronutrient supplements and pregnant women who consumed Fe+folate; and analyzed differences in mean hemoglobin levels among pregnant women who consumed multi-micronutrient supplements and Fe+folate at the 24th week of pregnancy.

METHOD

This was a quasi-experiment with a non-randomize community trial design and pre and post-test control group. The study was conducted in Banggai District in the work areas of 4 Community Health Centers, namely Kampung Baru, Simpong, Biak and Nambo in 2020. The number of samples involved in this study was 48 pregnant women, who were assigned in the intervention and control groups consisted of 24 pregnant women, respectively. The intervention group involved pregnant women who were administered with Multiple Micronutrient (MMN) supplements with composition based on the United Nations International Mutiple Micronutrient Antenatal Preparation (UNIMMAP) formula by Unicef-WHO-UN which contained 15 vitamins and minerals. Meanwhile, the control group was administered with Fe+Folate supplements (in accordance with the current health program for pregnant women).

The intervention in this study was carried out in a single blind manner with the aim of preventing response bias. Respondents in both groups did not know the difference in the interventions provided. The Fe+Folate supplement, which was originally in tablet form, is packaged in capsule form that resembles MMN (the packaging process was carried out by pharmacists).

The current study was conductes with strict assistance to ensure consumption compliance. Intervention and compliance monitoring were carried out every 14 days. The accompanying staff provided notifications via electronic messages to remind respondents of their compliance in consuming supplements every day.

Hemoglobin levels were assessed at the 12th and 24th week of pregnancy. Various characteristics such as age, occupation, education, physical activity, body mass index (BMI), intake of iron and vitamin C from food were assessed at study baseline. Assessment of hemoglobin levels used the Hemocue Hb 201 deviceIron and vitamin C intake from food was assessed through interviews using the Semi Quantitative-Food Frequency Questionnaire (SQ-FFQ). Furthermore, assessment of nutritional status (BMI) used the Anthropometric Kit. The researchers standardized the instruments and anthropometric skills of the measuring staff before conducting the study. Before interview regarding food intake, the researchers and research assistants got training. Analysis of nutritional intake was performed by trained nutrition staff using the nutrisurvey application. Sampling and analysis of hemoglobin levels were carried out by trained personnel using standardized methods and tools.

Data analysis was performed based on type, data measurement scale and data distribution. In general, data analysis applied the chi-square test, independent t test and dependent t test and non-parametric test. This study has obtained ethical approval from the Ethics Commission of the Faculty of Public Health, University of Indonesia.

RESULTS

Before providing intervention, a comparative analysis of the initial (baseline) characteristics in the two groups was first carried out. At the baseline, various characteristics of respondents were assessed, namely demographic characteristics (age, occupation, education), BMI and physical activity. Data were collected from 48 pregnant women from two subject groups (pregnant women who consumed MMN and pregnant women who consumed Fe+folate).

The mean age of pregnant women was 30.2 years. The youngest age of respondents was 20 years and the oldest age was 39 years. Most of respondents were housewives and had a high level of education (senior high school and college).

Table 1. Comparison of Demographic Characteristics, BMI and Physical Activity By Intervention Group at the Study Baseline

Characteristic of Respondents	MMN n(/%)	Fe+folate n(/%)	Total n(/%)	p-Value
Age Category*				
<20	0 (0.0)	0 (0.0)	0 (0.0)	0.739
20-35	19 (52.8)	17 (47.2)	36 (75.0)	
>35	5 (41.7)	7 (58.3)	12 (25.0)	
Occupation**				
Civil Servant/TNI/Police	2 (50.0)	2 (50.0)	4 (8.4)	0.082
Private	6 (85.7)	1 (14.3)	7 (14.6)	
Entrepreneur/Merchant/Service	0 (0.0)	3 (100.0)	3 (6.2)	
Housewife	16 (47.1)	18 (52.9)	34 (70.8)	
Education **				
No formal education	1 (100.0)	0 (0.0)	1 (2.1)	0.376
Elementary	3 (75.0)	1 (25.0)	4 (8.3)	
JHS	1 (50.0)	1 (50.0)	2 (4.2)	
SHS	7 (35.0)	13 (65.0)	20 (41.7)	
Diploma/Bachelor/Master	12 (57.1)	9 (41.9)	21 (43.8)	
BMI **				
<18.5 (Underweight)	1 (50.0)	1 (50.0)	2 (4.2)	1.000
≥18.5-<25 (Normal)	14 (50.0)	14 (50.0)	28 (58,3)	
≥25-27 (Overweight)	9 (50.0)	9 (50.0)	18 (37.5)	
Physical Activity*				
High(MET>3000)	11 (50.0)	11 (50.0)	22 (45.8)	0.273
Moderate(MET600-3000)	7 (70.0)	3 (30.0)	10 (20.8)	
Low(MET<600)	6 (37.5)	10 (62.5)	16 (33.3)	

**) Data were analyzed using the chi-square test.*
***) Data were analyzed using non-parametric statistical test*

The mean body mass index (BMI) indicated normal nutritional status with a fairly wide range. The lowest BMI was 17kg/m2 (underweight) and the highest BMI was 27kg/m2 (overweight/obese).

The respondents' physical activity at the baseline of the study was classified as heavy in both groups. However, it is also necessary to consider the fairly wide interval in physical activity scores in these two groups. There were no significant differences in iron and vitamin C intake variables between the two study groups. The hemoglobin levels before the intervention in both groups were normal with a mean of 11.6 g/dl.

Table 2. Comparison of Age, BMI, Physical Activity, Food Intake and Hemoglobin Levels by Intervention Group at the Study Baseline

Variable	MMN n(/%)	Fe+folate n(/%)	Total	p-Value
Age at time of study *	29.7 (20-38)	30.7 (23-39)	30.2 (20-39)	0.508
BMI *	23.5 (18-27)	23.9 (17-27)	23.7 (17-27)	0.529
Physical Activity Score *	3815.5 (120-12320)	2410.0 (120-6760)	311.7 (120-12320)	0.509
Iron Intake**	53.3 (13.78-95.0)	56,94 (13,78-300.63)	55.13 (13.78-300.63)	0.445
Vitamin C Intake **	163.2 (22.7-403.3)	184,22 (35.6-466.1)	173.76 (22.7-466.18)	0.734
Hemoglobin *	11.7 (9.9-14.0)	11,4 (8.2-14.3)	11.6 (8.2-14.3)	0.509

**) Data were analyzed using the chi-square test.*
***) Data were analyzed using non-parametric statistical test*

However, there were still some respondents with low hemoglobin levels. Based on comparative analysis, there were no differences in characteristics between the two study groups at the study baseline (p-value >0.05).

Table 3. Percentage of Compliance with Supplement Consumption by Study Group

Intervention Group	Mean (SD)	p*
Pregnant Women who were administered with MMN	85.9 (13.9)	0.607
Pregnant Women who were administered with Fe+Folat	86.5 (11.1)	

**) Data were analyzed using t-test.*

Furthermore, the level of compliance with supplement consumption in the two groups was also evaluated. The results of the analysis showed that a percentage of compliance in both groups of >85%. Based on independent t test analysis, there was no significant difference in the percentage of compliance between the two groups.

The mean hemoglobin levels in both groups decreased during the second trimester of pregnancy. In the group of pregnant women consuming MMN, the mean hemoglobin level in the 12th week of pregnancy was 11.7 g/dL (minimum Hb level was 9.9 g/dL and maximum Hb level was 14.0 g/dL). Such finding indicated a normal condition (non-anemic) of pregnant women. However, there were respondents with Hb levels of <11 g/dl (had anemia). No analysis was performed on the number of respondents who experienced anemia at the initial stage of the study (12th week of pregnancy).

Table 3. Differences in Mean Hemoglobin Levels During Pregnancy (12th week and 24th week) in both groups

Intervention Group	Time of Examination	Mean (min-max)	P *
Pregnant Women who were administered with MMN	12th week	11.7 (9.9-14.0)	0.143
	24th week	11.4 (8.9-13.3)	
Pregnant Women who were administered with MMN	12th week	11,4 (8.2-14.3)	0.408
	24th week	11.3 (9.3-13.3)	

**) Data were analyzed using t-test.*

The mean Hb level at the 24th week decreased to 11.4 g/dL (minimum Hb level was 8.9 g/dL and maximum Hb level was 13.3 g/dL). It can be seen that there were respondents who had quite low hemoglobin level by 8.9 g/dl. However, such decrease in Hb level was not statistically significant (p-Value> 0.05). In the group of pregnant women who consumed Fe+Folate, the mean Hb level at the 12th week of pregnancy was 11.4 g/dL (minimum Hb level was 8.2 g/dL and maximum Hb level was 14.3 g/dL). Such finding indicated that most of pregnant women had a normal Hb level of >11 g/dl. However, there were respondents in this group who experienced moderate anemia (Hb level of 8.2 g/dl) in the first trimester of pregnancy. No analysis was performed on the number of respondents who experienced anemia.

Table 4. Differences in Mean Hemoglobin Levels at the 24th Week of Pregnancy between the Intervention Groups

Intervention Group	Mean (min-max)	p*
Pregnant Women who were administered with MMN	11.4 (8.9-13.3)	0.415
Pregnant Women who were administered with Fe+Folat	11.3 (9.3-13.3)	

**) Data were analyzed using t-test.*

At the 24th week of pregnancy, the mean Hb level decreased to 11.3 g/dL (minimum Hb level was 9.3 g/dL and maximum Hb level was 13.3 g/dL). Although there was a decline in the group, individually there were several respondents who experienced an increasenin hemoglobin levels. Based on comparative analysis, the difference in mean hemoglobin levels was not statistically significant (p-Value >0.05).

At the end of the second trimester, the mean hemoglobin level of pregnant women who consumed MMN was higher than those who consumed Fe+Folate. However, such difference was not statistically significant (p-Value >0.05). In the group of pregnant women who consumed MMN, there were respondents with Hb levels that were much lower than in the group of pregnant women who consumed Fe+Folate. On the other hand, in this group there were also respondents with Hb levels that were higher than the highest Hb levels in the group of pregnant women who consumed Fe+Folate. Such finding showed a fairly high interval estimate of hemoglobin levels in the group of pregnant women who consumed MMN.

DISCUSSION

This was a non-randomized controlled quasi-experimental study. Compared to quasi-experimental without a control group or observational study, this type of study is superior and more convincing in studying the effect of the independent variable on the dependent variable.

Based on the results of this study, the mean hemoglobin levels of pregnant women in both study groups decreased during the second trimester. However, the difference was not statistically significant ($p>0.05$). In theory, micronutrient supplementation is effective in increasing the hemoglobin levels of pregnant women as found in a study conducted by Royani, (2013)[9]. Likewise, a study conducted by Sosiloningtyas in 2012 showed that administration of Fe+folate tablets per day to pregnant women for 13 weeks could reduce anemia rates and increase pregnant women's iron level.

A decrease in hemoglobin levels found in this study could be due to several factors during pregnancy[10]. Iron deficiency often occurs during pregnancy since iron requirement increases twice the requirement before pregnancy. This happens because the blood volume increases by up to 50% during pregnancy and causes hemodilution which is commonly known as physiological anemia in pregnancy which often occurs at 24-32 weeks of pregnancy. The increase in total blood volume begins early in the first trimester and then increases rapidly until mid-pregnancy[11]. At the beginning of pregnancy in the first trimester, pregnant women usually experience excessive hyperemesis. Excessive hyperemesis can affect hemoglobin levels[12]. Mothers with higher grade hyperemesis gravidarum tend to have more severe anemia[13]. Hyperemesis that occurs continuously can cause dehydration due to lack of fluid consumed and loss of fluid due to vomiting. As a result, extracellular fluid and plasma are reduced so that the volume of fluid in the blood vessels aa well as blood flow to the tissues decrease. Such condition further lead to a decrease in the amount of food substances (nutrients) including iron and oxygen to be delivered to the tissues. So, even though multimicronutrient supplements are given, it is not optimal for producing red blood cells and may cause a decrease in hemoglobin levels (anemia).

It is expected that providing multi-micronutrients based on UNIMMAP formula can anticipate the problems mentioned above. MMN not only contains iron but also contains 15 types of vitamins and minerals which are very important for pregnant women and also help the absorption of nutrients. Although multi-micronutrient supplements only contain 30 mg of iron (lower than the iron content in the Fe+Folate formula), they have various advantages and have gone through various clinical trials regarding their positive and negative impacts on health. Various studies revealed that the absorption level of the ferrous form of iron (Fe^{++}) used in this formula was higher than the ferric form (Fe^{+++}); Iron absorption in multi-micronutrient supplement formulations was higher (compared to Fe+Folate) due to the presence of Vitamin C, vitamin A, and riboflavin; The addition of 60 mg of iron should be accompanied by at least 30 mg of zinc to avoid possible negative effects on iron absorption; the addition of iron could increase the total amount of metal, which could increase negative side effects; Lower iron content sufficient if consumed regularly, as it could reduce certain side effects (eg, constipation); Excessive iron level would increase susceptibility to some infections; Almost all pregnant women experienced mild or moderate anemia, which can be treated with 30 mg of iron[14].

In this study, the mean hemoglobin level in the group of pregnant women who consumed MMN was higher than the group of pregnant women who consumed Fe+folate. The difference in the mean hemoglobin levels between the Multiple Micronutrient and Iron Folate groups was 0.1 g/dL, which was not statistically significant. Likewise, a study conducted by Monoarfa in 2018 showed that the mean hemoglobin levels in the Multiple Micronutrient group was higher than those in the Iron Folate group, but this difference was not statistically significant ($p=0.994$)[15]. The difference in the mean hemoglobin levels between the Multiple Micronutrient and Iron Folate groups was 0.2 g/dL[15]. This little difference could be due to initially normal Hb levels of women who consumed multi-micronutrient supplements before the intervention. Thus, when the intervention was performed, the mean hemoglobin level remained the same and could decrease due to hemodilution.

The provision of nutritional supplements will be more effective if given to groups experiencing health problems related to the deficiency of those nutrients. An intervention study on micro-nutrients and DNA damage yielded varied results, influenced by factors such as nutritional status and health at the time of administration[16]. A systematic review conducted by Keats, et al in 2019 indicated a decreased risk of giving birth to underweight babies, with a reduction of up to 19% in mothers with anemia, 12% in underweight mothers, and a decrease of 16% in mothers with insufficient weight during pregnancy[17]. This study did not conduct a stratified analysis based on anemia status, health conditions, and other characteristics of pregnant women theoretically linked to changes in hemoglobin levels during pregnancy.

Insufficient iron intake in the body can also be caused by factors inhibiting iron absorption, such as the habit of drinking tea while eating[18-20]. According to Proverawati (2013), drinking tea at least an hour before or after eating will reduce the absorption capacity of blood cells for iron by 64%[21]. The reduction in absorption capacity caused by tea is higher than the effect caused by drinking a glass of coffee after eating, wherein coffee only reduces absorption capacity by 39%. The reduction in iron absorption is caused by the tannin content in tea which binds minerals[21]. In this study, it was found that the majority of respondents had the habit of consuming tea. However, the researchers did not ask about the time of tea consumption.

Apart from Banggai District, large multi-micronutrient supplementation trials or projects have been conducted in various countries and in Indonesia since 1990 (approximately 23 decades). Therefore, the efficacy and effectiveness of multi-micronutrients in treating anemia and various health problems of pregnant women and babies has been tested in various studies. Furthermore, 12 efficacy trials and 6 effectiveness trials were conducted by UNICEF in 12 countries covering 3 continents (Asia, Africa and America) with the aim of improving micronutrient status, gestational age at birth and reducing the rates of stillbirths and neonatal deaths[22]. A systematic review and meta-analysis confirmed the effect of multi-micronutrient administration in reducing the risk of low birth weight, premature birth, and preterm pregnancy. A Cochrane review conducted by Keats et al. in 2019 identified 20 trials (141,849 women) which concluded that, compared with iron supplementation with or without folic acid, daily multi-micronutrient supplementation during pregnancy could reduce the risk of low birth weight and preterm pregnancy in low and middle income countries. Likewise, deaths at birth and neonatal deaths were slightly lower in the MMN group[16]. Moreover, a meta-analysis conducted by Smith et al. in 2017 consisted of 17 randomized trials in low and middle-income countries also found greater survival effects and birth outcomes from hmicronutrient supplementation with high adherence (≥95%) to supplementation[23]. This meta-analysis showed a subgroup of pregnant women who might experience greater benefits from antenatal multiple micronutrient supplementation compared with folic acid supplementation alone. Among anemic women, multiple micronutrient supplementation resulted in greater reduction in the risk of low birth weight (−19%), non-term pregnancy (−8%), and death of infants aged 6 months (−29%) compared to non-anemic women anemia. Among underweight women (BMI <18.5 kg/m^2), multiple micronutrient supplementation reduced the risk of preterm birth by 16%. Furthermore, initiation of multiple micronutrient supplementation before 20 weeks gestation reduced the risk of preterm birth (11%) and high compliance (≥95%) reduced the risk of infant death (-15%)[23].

There were several limitations that might cause bias in this study. This study did not apply a randomization procedure in allocating subjects to each group. This could lead to subject selection bias, thus influencing the generalization of study results. In addition, the number of samples in this study was not calculated based on differences in proportions or differences in mean homoglobin levels between the group of women who consumed MMN and Fe+Folate, thereby reducing research power and external validity. Im addition, data analysis section did not analyze differences in hemoglobin levels between the two groups by anemia status at the baseline of the study and various characteristics that are theoretically related to hemoglobin levels of pregnant women which might have a modifying effect of MMN consumption on hemoglobin levels of pregnant women.

CONCLUSIONS

The mean hemoglobin levels of pregnant women in both study groups decreased during the second trimester. During the second trimester of pregnancy, the mean hemoglobin level in the intervention group who were given MMN decreased by 0.3 g/dl (p-value=0.143) and in the control group who were given Fe+Folate decreased by 0.1 g/dl (p-value=0.408). The difference in the decrease was not statistically significant. At the 24th week of pregnancy, the mean hemoglobin level of pregnant women who were given MMN was 0.1 g/dl higher than those who were given Fe+Folate. Such difference was not statistically significant (p-value=0.415).

There is a need to conduct further study to strengthen the evidence on the effect of MMN administration since early pregnancy and during the preconception period on hemoglobin levels. The further experimental study should appl a randomization procedure in subject allocation with an appropriate sample size to ensure external validity. Further study is recommended to determine the effect of MMN and Fe+Folate on hemoglobin levels by considering anemia status, characteristics of pregnant women and other health status before intervention is carried out.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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