EXECUTIVE SUMMARY

THE EFFECTIVINESS OF IRON FOLIC ACID SUPPLEMETATION PROGRAM IN REDUCING ANEMIA AND STUNTING PREVALENCE IN INDONESIA: A META-ANALYSIS

arranged by:
Secretariat of the Vice President of the Republic of Indonesia

INTRODUCTION

Until today, anemia is still a major nutritional problem in Indonesia. Most of the anemia problems in Indonesia and various countries in Asia and Africa are caused by iron deficiency. Although the government has implemented programs to overcome anemia problems with the main program of iron folic acid supplementation since 1970, the problem of anemia is remaining high. The results of Basic Health Research (*Riskesdas*) in 2018 from the Research and Development Agency of the Ministry of Health of the Republic of Indonesia, reported that the prevalence of anemia in pregnant women in Indonesia has increased by almost 10% compared to the previous national survey (*Riskesdas,* 2013), from 37.1% to 48.9%. Another fact of survey result revealed that 84.6% of pregnant women with anemia are in the young age group (15-24 years). This means that pregnant young women have a higher risk of anemia than women in another age group. Therefore, young women are one of the important targets in overcoming anemia in Indonesia. The 2018 *Riskesdas* did not provide information on the magnitude of the anemia problem in adolescent girls, but only provides data on the coverage of blood supplementation tablets and their very low consumption.

Since 2017, the Indonesian government has paid more attention to the high prevalence of stunting, so that prevention of stunting has become one of the national priorities in an effort to accelerate the improvement of nutrition in Indonesia. Efforts to accelerate nutrition improvement are focused on the first thousand days of life of a child. Meanwhile, the distribution of iron folic acid supplementation program with universal coverage for all pregnant women is expected to be one form of specific intervention within the framework of an integrated accelerated stunting prevention program. This program is expected to be an effective program in reducing the prevalence of anemia in pregnant women, as well as improving pregnancy outcomes, particularly in reducing stunting rates in Indonesia.

There have been many studies on anemia and / or stunting that have been carried out scattered in various regions in Indonesia, but there is no single study that can provide conclusions to describe the problems related to anemia and the iron folic acid supplementation program in Indonesia. Therefore, it is necessary to conduct a systematic review and meta-analysis of several publications in various journals on the impact and effectiveness of the iron folic acid supplementation program on reducing the prevalence of anemia and reducing the prevalence of stunting in Indonesia. The Vice President Secretariat's Secretariat for the Acceleration of Prevention of Stunted Children (TP2AK) Team in collaboration with a research team from the Health Studies Unit, Faculty of Public Health, Universitas Airlangga aims to conduct this study.

PURPOSE OF STUDY

General Purpose

Produce recommendations and policy suggestions for improving iron folic acid supplementation programs based on a literature review of iron deficiency anemia prevention programs among pregnant women and adolescent girls.

Specific Purpose

1. Conducted a literature review on the level of compliance in taking iron folic acid tablet and its influencing factor among pregnant women and adolescent girls
2. Conducted a literature review on the efficacy of iron tablet on:
    a. Hemoglobin levels in pregnant women and adolescent girls
    b. Birth weight and birth length
    c. Premature birth
    d. Neonatal mortality

METHODS

This study uses systematic review and meta-analysis methods [1-4]. The study was preceded by a systematic literature review of the several research on the use of iron folic acid supplement in Indonesia, and their effect on anemia and pregnancy outcome. Literature searches using relevant keywords through various database such as PubMed, web of science for literature published in international journals. For articles published in national journals, searches were made through *Portal Garuda*, *Neliti.com*, and university library repositories in Indonesia. Literature search was carried out since August 2020. After screening 8,325 articles using the

COVIDENCE software, 1,857 articles were found to be relevant to be selected for eligibility following the PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-analyses*) diagram [5]. From the selection process, 545 eligible articles (538 from Covidence + 7 articles that did not enter Covidence) were obtained for further analysis (Figure 1). After conducting a review and assessment of the quality of the articles, high quality articles were selected to be analyzed further in meta-analysis.

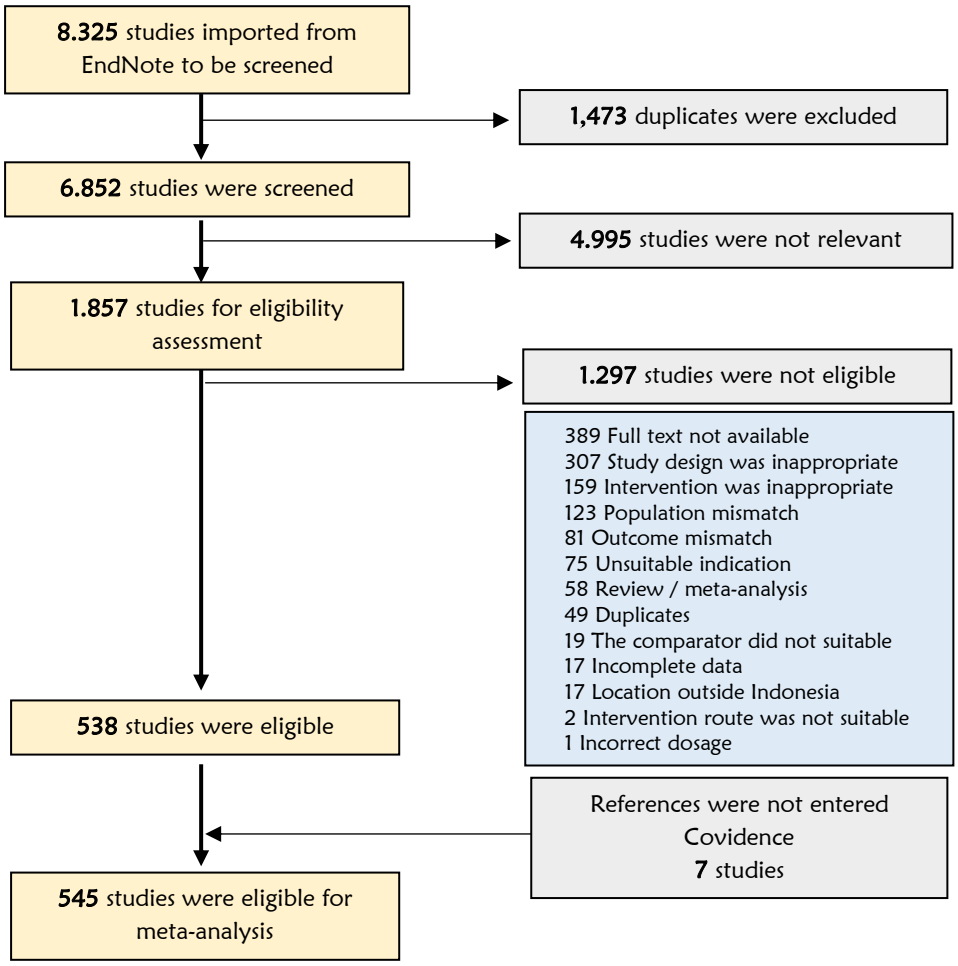

Figure 1. PRISMA diagram depicting the flow of article selection

STUDY RESULTS

Several important findings in this study can be used as input for improving anemia control and stunting prevention programs in Indonesia, including: 1) The prevalence of anemia in pregnant women and adolescent girls; 2) Factors that influence compliance in consuming iron-folic acid tablets among pregnant women and adolescent girls; 3) The importance of counseling and education in the iron folic acid supplementation program; 4) Husband and family support in increasing compliance with iron folic acid tablets consumption; 5) Consumption of iron folic

acid tablets accompanied by fruit / vegetables and micronutrients also multiple-micronutrients (MMN) and their effect on hemoglobin levels and pregnancy outcome.

1. Prevalence of Anemia

Result of research in various regions in Indonesia shows that the prevalence of anemia in pregnant women ranges from 20% - 93.8% with mean of 52.87%. The lowest prevalence of anemia was found in studies conducted on first trimester pregnant women, while the highest prevalence was found in studies targeting third trimester pregnant women. This means that the increasing gestational age, the higher the prevalence of anemia. Meanwhile, the prevalence of anemia in adolescent girls ranged from 24% - 65.7%, with a mean of 40.3%. This prevalence is higher than the national data from the 2013 and 2018 basic health survey, and the 2017 IDHS results reported only 23% (Table 1).

Table 1. Compliance of taking iron folic acid tablet and prevalence of anemia in pregnant women and adolescent girls in Indonesia

Population	Data source	Compliance of iron folic acid tablet intake	**Prevalence of anemia**
Pregnant women	Literature review (year 1994 to 2020)	32% - 62.7%	20% - 93.8%
	Basic health survey (*Riskesdas)* 2018	Consumption < 90 tablets: 61,9% ≥ 90 tablets: 38,1%	48.9%
Adolescent girls	Literature review (year 2007 to 2020	Iron-folic supplement program: 5% - 56% Commercial products: 90-97%	24% - 65.7%
	Basic health survey (*Riskesdas)* 2018 and IDHS 2017	Consumption < 52 tablets: 98,4 ≥ 52 tablets: 1,6%	23%

The cause of anemia is often associated with compliance with iron tablets consumption. The compliance criteria were measured based on the number of iron tablets consumed. Pregnant women are advised to consume at least 90 tablets a year, while adolescent girls are advised to consume at least 52 tablets per year. If pregnant women or adolescent girls did not take iron tablets as recommended, the chances of experiencing anemia will be even greater. If

anemia occurs during pregnancy, it can also affect pregnancy outcomes, such as an increased risk of preterm birth, low birth weight, bleeding, also maternal and infant mortality.

2. Compliance of iron Folic Acid Tablet Intake and Influencing Factors

a. Compliance of Pregnant Women

One of the biggest obstacles to the success of the iron folic acid supplementation program is the compliance of pregnant women and adolescent girls in consuming iron folic acid tablets. The results of literature search showed that the compliance of pregnant women in consuming iron tablets from government ranged from 32% - 62.7%. The adherence of iron folic acid tablet consumption in pregnant women was higher than adherence in adolescent girls. Information about adherence taking iron folic acid tablets and its influencing factors was obtained from various cross-sectional studies.

Knowledge of pregnant women, family support, side effects and boredom or forgetfulness were the most studied factors related to maternal compliance in consuming iron folic acid tablets. Observed from the number of studies, factors related to the level of compliance of pregnant women in consuming iron folic acid tablets were consecutively the level of pregnant women knowledge about anemia and iron folic tablets, followed by the support of husbands and parents. Therefore, nutrition education and personal counseling for pregnant women are very important to increase knowledge, they need to be included in complementing the iron folic acid supplement program through antenatal services.

b. Compliance of Adolescent Girls

Adherence to consuming iron folic acid tablets among adolescent girls was mainly related to the side effects after consuming such as nausea / vomiting / dizziness, as well as aspects of the quality and appearance of supplement products. The adolescent girls targeted by the program are junior and senior high school students. Most of the schoolgirls refuse to take the iron folic acid tablet from the government (*Kimia Farma Production*). This is indicated by the data from the literature review which reveal the level of compliance of taking iron folic acid tablets from government was very low (5-56%), even basic health survey data reported only 1.6% girls who consume iron folic acid tablets >52 tablets in a year. The iron folic acid supplement program for adolescent girls was done by given one tablet once a week through School's Health Clinic (*Unit Kesehatan Sekolah*). The involvement of teachers and the use of cards or other tools used in recording and monitoring can increase compliance of iron folic acid tablet consumption for students. Therefore, the role of the teacher is very important to motivate in taking iron folic acid tablets. Another finding in this study was that adolescent girls

prefer commercial supplement products because of less frequent side effects after consuming, which resulting in higher adherence (90-97%) [6-31].

The iron folic acid tablets from the government contains 60 mg of elemental iron and 0.4 mg of folic acid. On the other hand, commercial iron that is sold freely on the market contains about 250 mg of ferrous gluconate (equivalent to 30 mg of elemental iron), 1 mg of folic acid, and some other vitamins and minerals such as 0.2 mg of manganese, 0, 2 mg copper, 50 mg vitamin C, and 7.5 mcg vitamin B12.

The coverage of iron folic acid supplement program for adolescent girls reached 76.2% (*Riskesdas*, 2018), but only 1.6% of students who complied to take the tablets. Meanwhile, if the iron folic acid supplement from the government is replaced by commercial products could significantly increase compliance. The note is that the commercial products given to students not only contain iron and folic acid, but contain various vitamins and minerals. Thus, an important issue related to the effectiveness of the iron folic acid supplement program for adolescent girls will be: whether the government emphasizes the aspect of program coverage or the compliance of taking iron folic acid tablets?

The coverage of iron folic acid supplementation is an indicator of program success measured by the number of recipients compared to the target. High coverage indicates that iron tablets have been distributed to the target. In contrast to compliance which measured from the intake of iron tablet received by the target whether it has been consumed according to the recommended amount or not. So far, the evaluation of coverage and compliance only includes iron tablets obtained from the Government Program without taking into account the coverage and compliance of commercial iron tablet consumption.

3. The importance of Counseling and Education Accompanying Iron Supplementation Program

Knowledge of pregnant women related to anemia and iron tablets were the main factors related to compliance in consuming iron tablets. In addition, support from husbands and families also plays a role in determining whether or not pregnant women are compliant with iron tablets. Therefore, enrichment of insights through nutrition education and personal counseling is very important so that pregnant women can increase their knowledge, then, compliance of iron tablet consumption can also be improved. Providing education on anemia and iron supplement needs to be included in antenatal care.

Educational interventions with various media such as flipcharts, short message (SMS) reminders, booklets, and personal counseling can increase the compliance of taking iron folic acid tablets, both in pregnant women and adolescent girls. Meanwhile, the factors that cause pregnant women did not consume iron folic acid tablets are forgetfulness / laziness / boredom,

as well as side effects i.e., nausea, vomiting, dizziness. Counseling and education using various media can improve this condition [6-10,32]. The results of a meta-analysis of the effects of educational interventions on adherence in taking iron folic acid tablets can be seen in Figure 2.

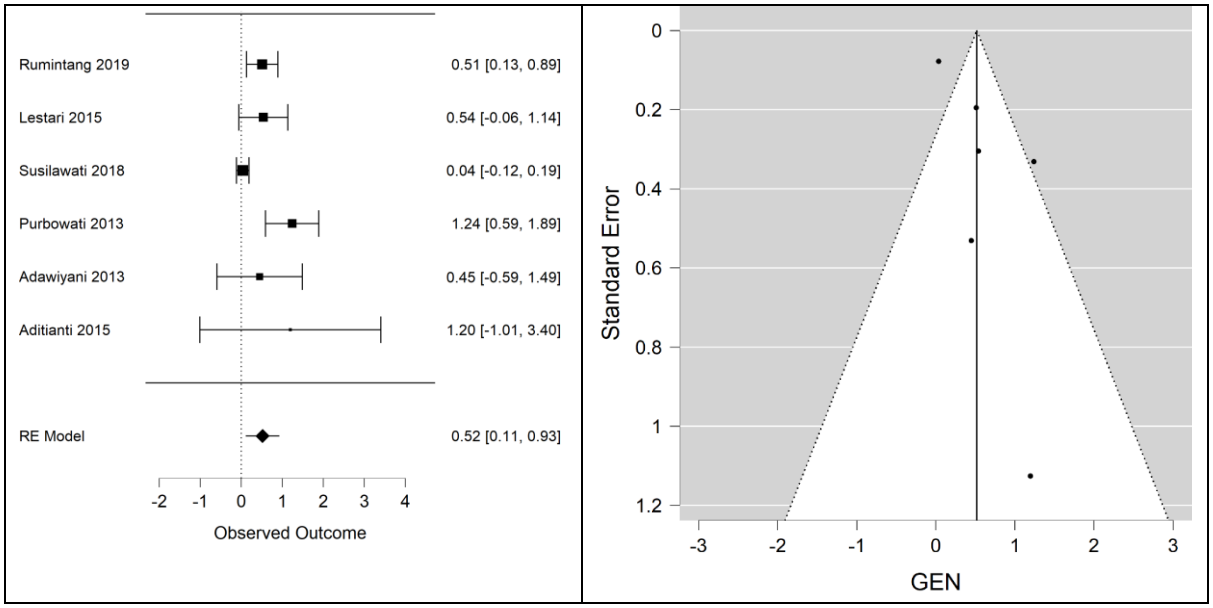

Figure 2. Meta-analysis result of the effects of various educational interventions and the compliance of iron folic acid tablet consumption

There were 6 (six) studies that qualified for a meta-analysis. The total effect size resulted from six studies showed a significant positive relationship (OR = 1.68, 95% CI = 1.12-2.52, p = 0.012) which proved that educational interventions increased compliance of taking iron folic acid tablets.

4. Husband and Family Support

The role of husband and other family members is the second important factor, which affects compliance in taking iron folic acid tablets in pregnant women. There were 10 (ten) studies on the role of the husband, and 11 (eleven) studies on the role of the family that qualified for a meta-analysis [11-27]. The results of the meta-analysis showed a significant positive relationship between the two analyzes (Figure 3 and Figure 4).

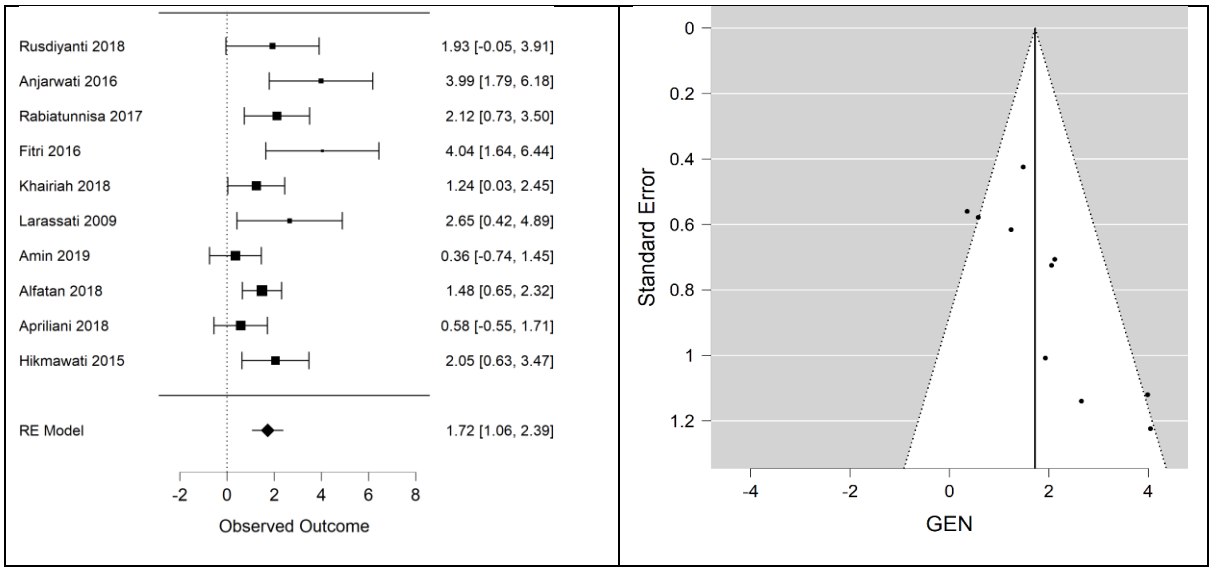

Figure 3. Meta-analysis result of the relationship between husband's support and the compliance of iron folic acid tablet consumption

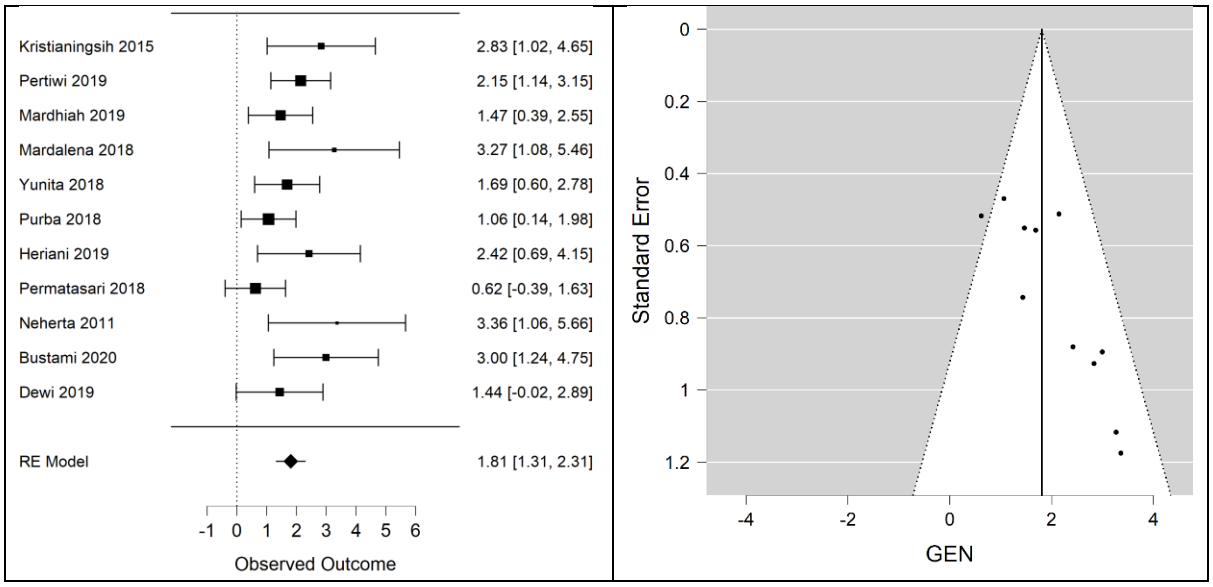

Figure 4. Meta-analysis result of the relationship between family support and the compliance of iron folic acid tablet consumption

The forest plot in Figure 3 indicates the total effect size resulting from ten studies in Indonesia shows a significant positive relationship between husband support and the compliance of iron folic acid tablet consumption (OR = 5.6, 95% CI = 2.89-10.87, p <0.0001). In addition, the importance of family support in influencing the compliance of pregnant women in consuming iron folic acid tablets was strengthened by the results of a meta-analysis of 11 studies in Indonesia (Figure 4). The total effect size resulting from the eleven studies showed a significant positive relationship as well (OR = 6.11, 95% CI = 3.69-10.10, p <0.0001).

5. Consumption of Fruits and Vegetables Strengthens the Effects of Iron Folic Acid Tablets in Increasing Hemoglobin (Hb), but Does Not Prevent Anemia

Consumption of fruits or vegetables along with iron folic acid tablet consumption has a large and significant effect on increasing hemoglobin levels. There were 13 studies on the effect of iron folic acid tablet consumption along with fruit or vegetable consumption in increasing hemoglobin levels, which were included in the meta-analysis [33-46].

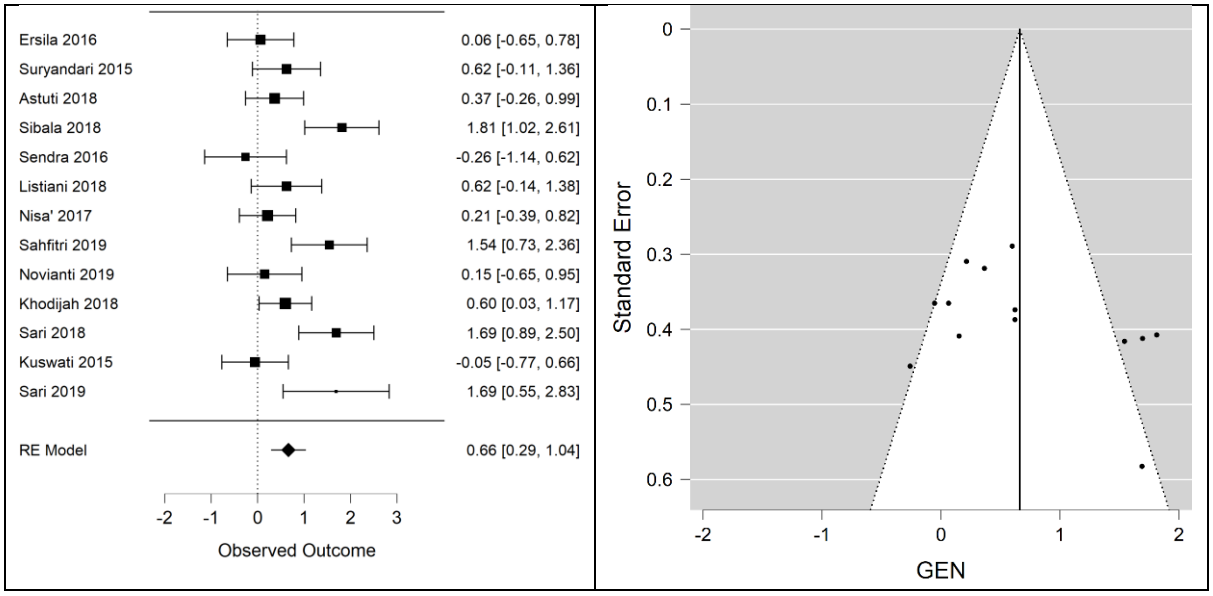

Figure 5. Meta-analysis result of the effect of adding fruit or vegetables to iron folic acid tablet on Hb levels

Based on paper selection process, we found 13 studies (1 RCT and 12 quasi-experimental studies) regarding the efficacy of added fruits or vegetables accompanying consumption of iron folic acid tablet compared to consumption of iron folic acid tablet alone. The results of the meta-analysis showed that the total effect size generated from all studies in influencing hemoglobin levels showed significant moderate positive effects (Standardized Mean Difference = 0.66; CI 0.29 to 1.04, p <0.001).

Of the various types of fruits and vegetables studied, guava juice, beet juice, papaya juice and spinach and honey combined juice showed a positive impact. The addition of guava juice, in particular, gave positive results that were quite consistent in increasing Hb levels. Although it can significantly increase the Hb level, this intervention cannot reduce the incidence of anemia. The result of the meta-analysis was shown in Figure 6.

Selection of articles using Covidence software resulting 3 study titles on the efficacy of added fruits or vegetables on the iron folic acid tablet in prevent anemia, compared to

consumption of iron folic acid tablet alone. The total effect size generated from all studies in influencing the risk of anemia showed a moderate positive effect but not significant (Standardized Mean Difference = 0.25; CI -0.45 to 0.96; p = 0.48). More studies are still needed to confirm these results.

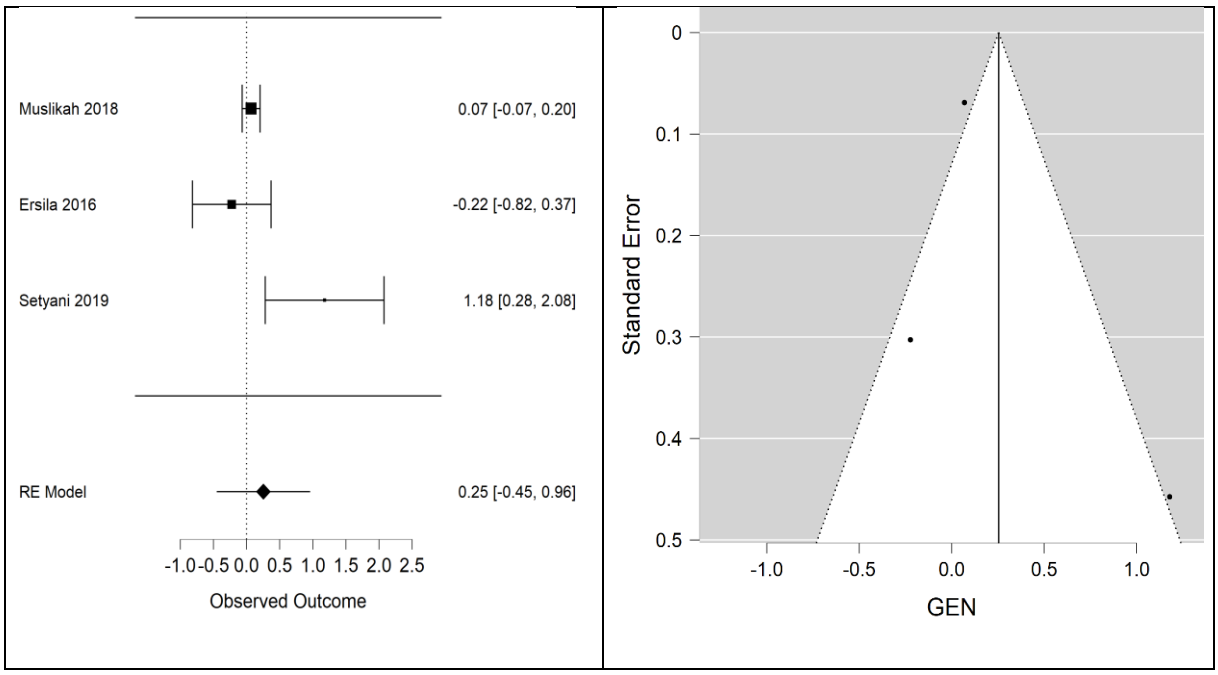

Figure 6. Meta-analysis result of the effect of adding fruits or vegetables to iron folic acid tablet on reducing the incidence of anemia

6. The Effect of Micro-Nutrients Addition on Iron Folic Acid Tablets Consumption on the Increase in Hb Levels

The addition of various micronutrients could have a better effect on increasing hemoglobin level, compared to consuming iron tablet alone. The most studied micronutrients are vitamin C (17 studies), Zn (3 studies), and vitamin A (9 studies) [47-65]. This scientific evidence can provide a discourse that pregnant women in Indonesia may not only be deficient in iron, but also deficient in other micronutrients.

a. Addition of Vitamin C

The screening process found 17 studies (5 RCT studies and 12 quasi-experimental studies) on the efficacy of adding Vitamin C to iron folic acid tablet compared to iron folic acid tablet alone, Figure 7 shows a meta-analysis result of 17 studies which describe that the total effect size resulted from all studies in influencing hemoglobin levels showed a profound and significant positive effect (Standardized Mean Difference = 0.63; CI 0.28 to 0.98, p <0.001).

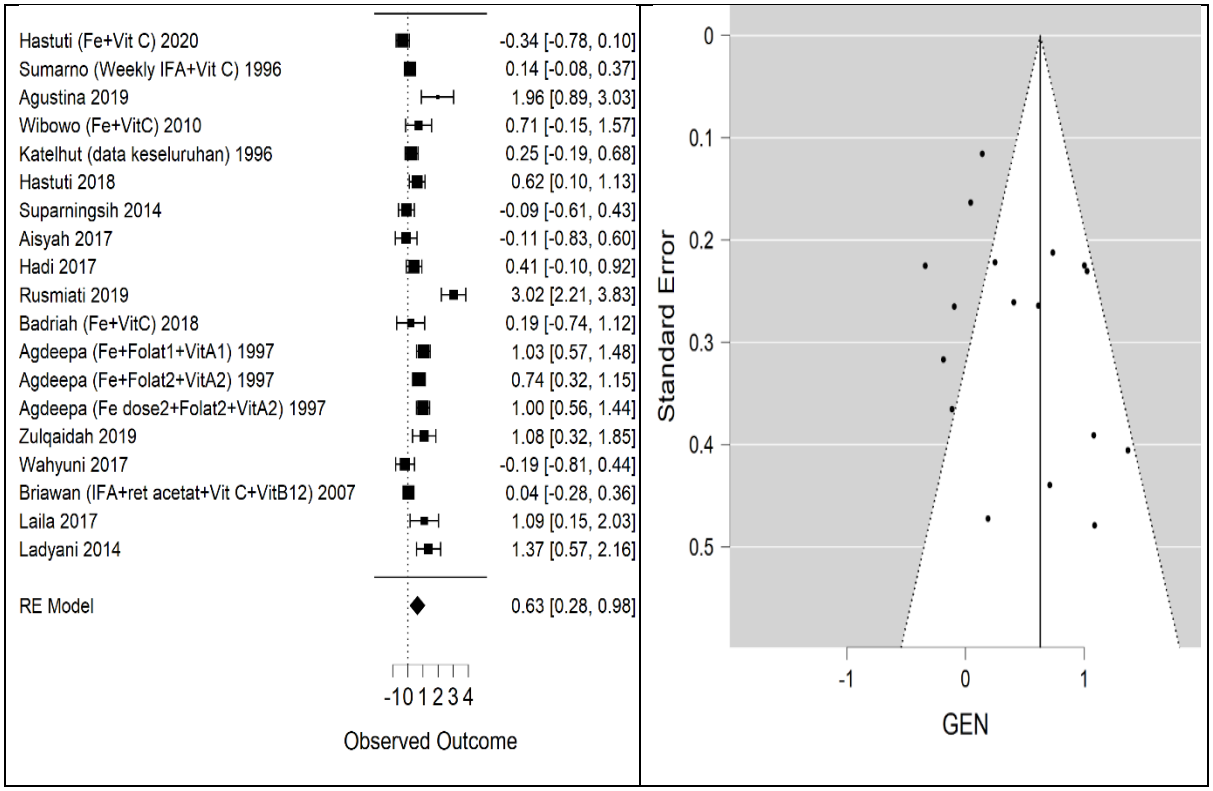

Figure 7. Meta-analysis result of the effect of adding vitamin C to iron folic acid tablet on hemoglobin level

An interesting finding is the analysis of the sub-group of pregnant women (9 studies) and the sub-group of adolescent girls (8 studies). The effect of the vitamin C addition on increasing Hb levels is greater in pregnant women than adolescent girls. Further results of the meta-analysis can be seen in Figure 7a and Figure 7b.

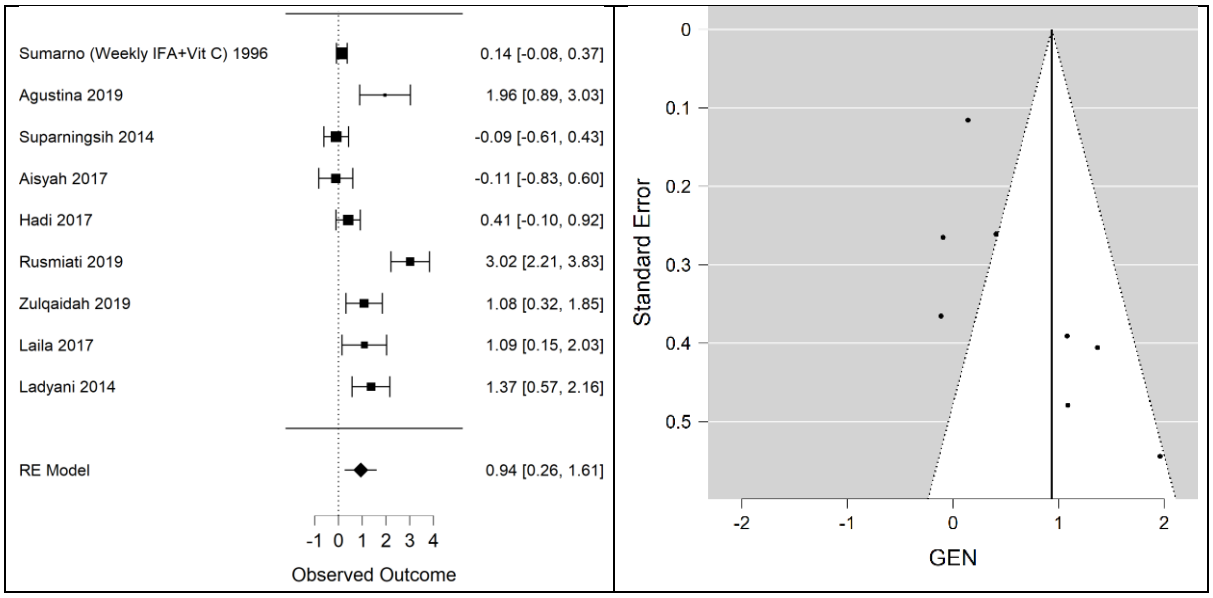

Figure 7a. Meta-analysis result of the effect of adding vitamin C to iron folic acid tablet on hemoglobin level in pregnant women

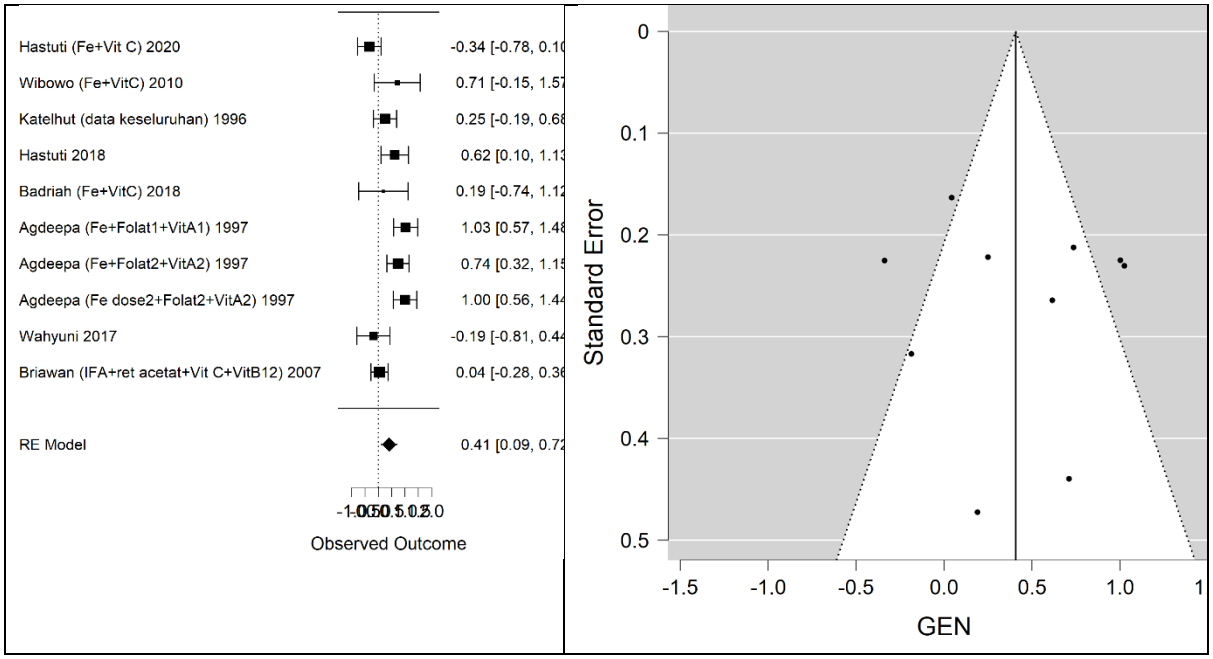

Figure 7b. Meta-analysis result of the effect of adding vitamin C to iron folic acid tablet on hemoglobin level in adolescent girls

Nine studies on pregnant women revealed that the effect of adding Vitamin C to iron folic acid tablet significantly increase hemoglobin levels in higher level (Standardized Mean Difference = 0.94; CI 0.26 to 1.61, p = 0.007). Although these 9 studies were not homogeneous, publication bias was low. Meanwhile, a meta-analysis of 8 studies on adolescent girls showed that the effect of adding Vitamin C to iron folic acid tablets in increasing hemoglobin levels was moderate (Standardized Mean Difference = 0.41; CI 0.09 to 0.72, p =

0.01). Differences in the body's response to the addition of vitamin C in pregnant women and adolescents girls might explain it, especially due to physiological changes in pregnant women. During pregnancy, the physiological condition of the mother causes an increase in the effectiveness of absorption, thus, the addition of vitamin C, which is also an enhancer factor, can increase the effectiveness of iron absorption both from supplements and from food.

b. Addition of Zinc (Zn)

There were 3 studies that qualified for this meta-analysis topic. Figure 8 shows the results of a meta-analysis of three studies on the effect of adding zinc (Zn) to iron folic acid tablet in increasing Hb levels [66]. The total effect size resulting from the three studies in influencing hemoglobin levels showed a small positive but insignificant effect (Standardized Mean Difference = 0.17; CI -0.11 to 0.45, p = 0.23).

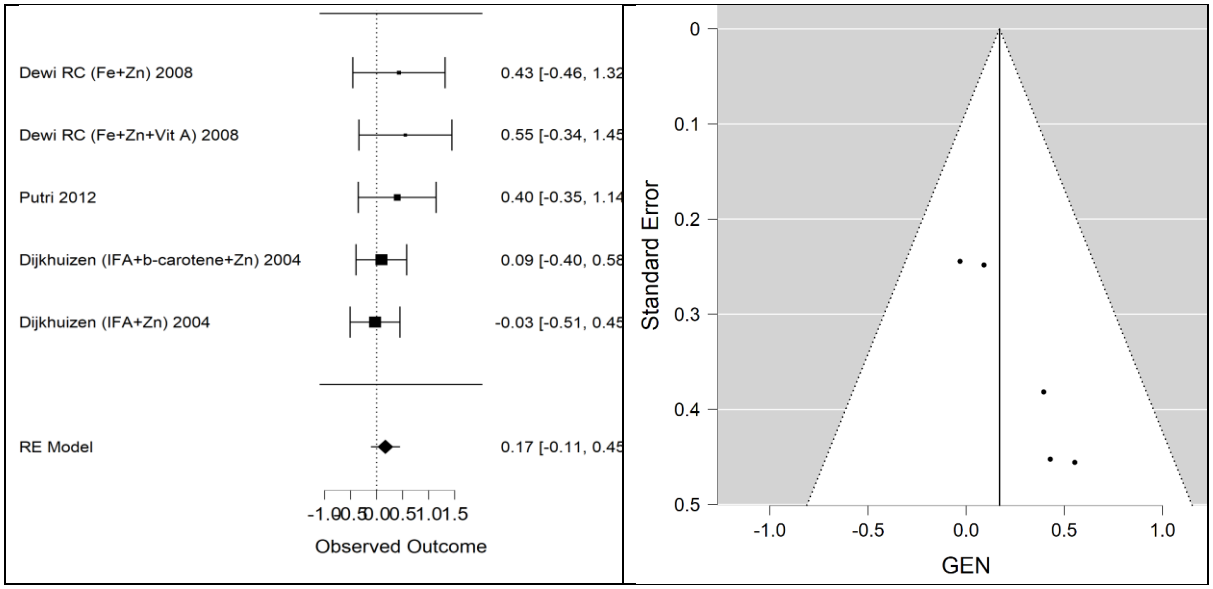

Figure 8. Meta-analysis result of the effect of adding Zinc to iron folic acid tablet on hemoglobin level in pregnant women

The addition of Zn supplements as a single nutrient at the same time as taking iron folic acid tablet, or as a formula added to the iron tablet had a positive impact on increasing Hb levels, although it was less effective.

c. Addition of Vitamin A

The results of the article selection found 9 studies on the efficacy of adding Vitamin A or beta carotene to iron folic acid tablet compared to iron folic acid alone. Of the nine studies, 8 studies were RCT studies and 1 study with quasi-experimental study. The result of the meta-

analysis is presented in Figure 9. The forest plot in Figure 9 indicate that the total effect size resulting from all studies in influencing hemoglobin levels shows moderate significant positive effects (Standardized Mean Difference = 0.58; CI 0.09 to 1.06, p = 0.02).

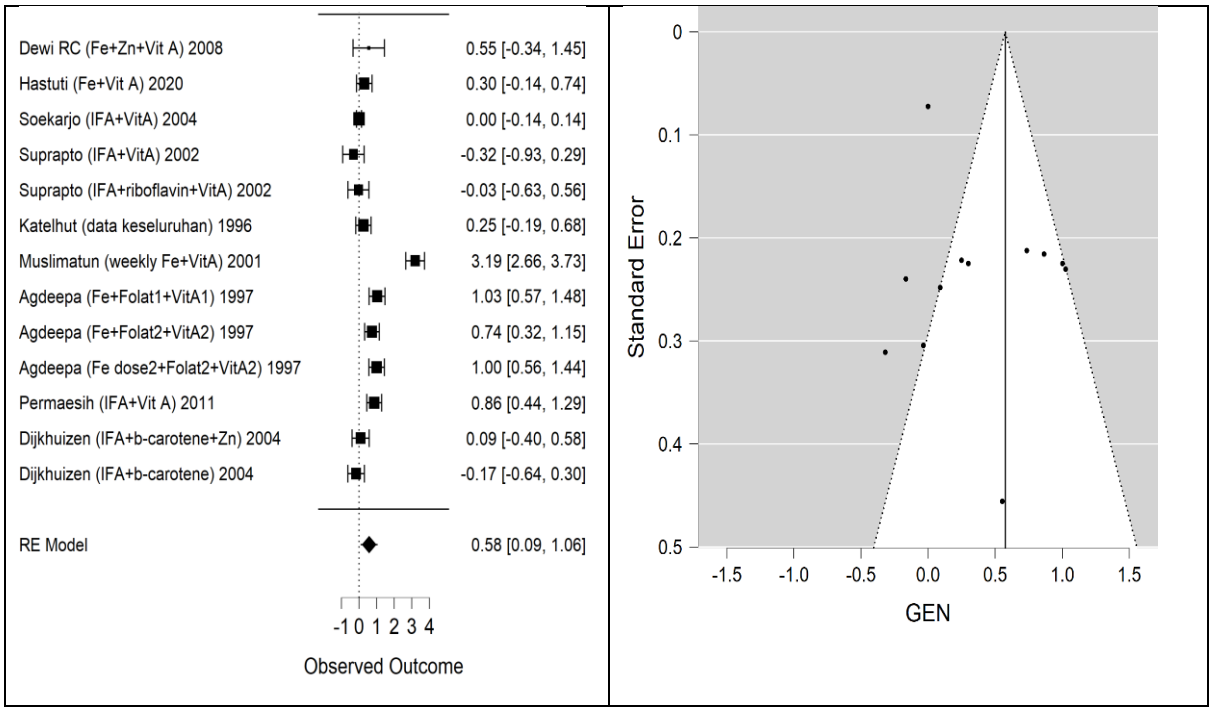

Figure 9. Meta-analysis result of the effect of adding vitamin A to iron folic acid tablet on hemoglobin level

From the total of 9 studies on the effects of vitamin A supplementation, 4 studies were conducted on pregnant women and 5 studies were conducted on adolescent girls. The analysis of the sub-group of pregnant women and the sub-group of adolescent girls gave different results. Figure 9a shows the results of a meta-analysis of 4 studies in pregnant women. The results revealed that the effect of adding Vitamin A to iron folic acid tablet was moderate, but not significant in increasing hemoglobin levels (Standardized Mean Difference = 0.55; CI -0.52 to 1.63, p = 0.31). Meanwhile, Figure 9b shows a meta-analysis result of 5 studies in adolescent girls which revealed that the effect of adding Vitamin A to iron folic acid tablet has a moderate and significant increase in hemoglobin levels (Standardized Mean Difference = 0.57; CI 0.25 to 0.89, p <0.001). Thus, a significant effect on the combined meta-analysis was contributed from 5 studies in adolescent girls. Hemodilution factor during pregnancy might cause a smaller effect of vitamin A addition compared to adolescent girls.

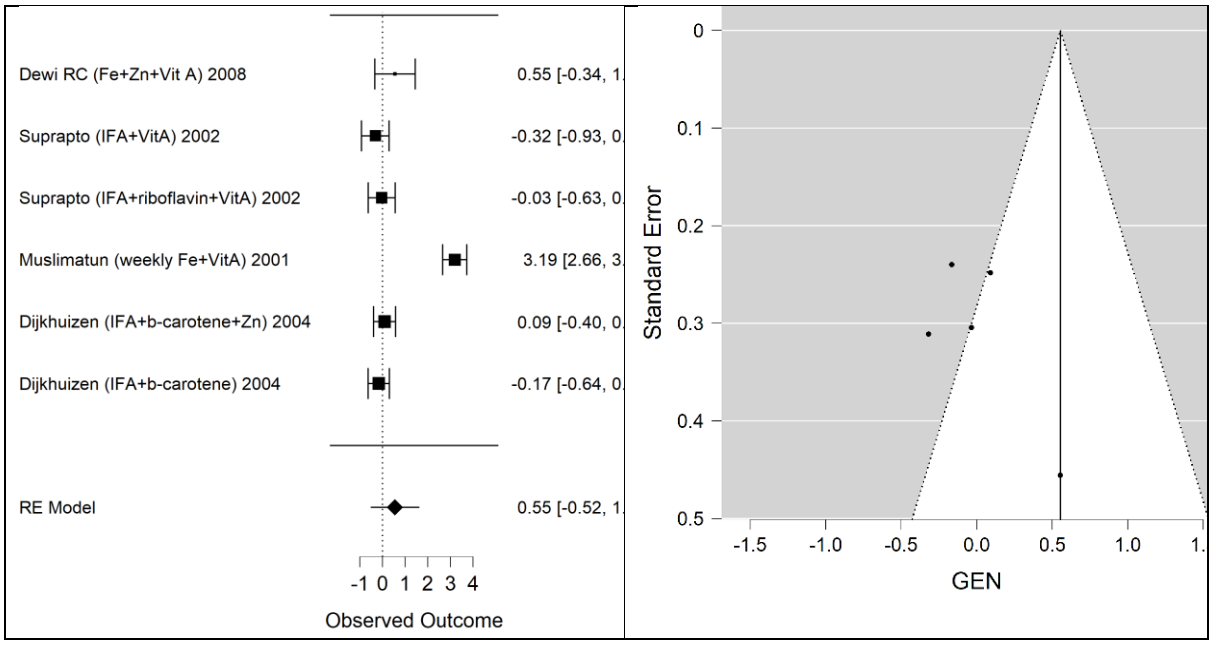

Figure 9a. Meta-analysis result of the effect of adding vitamin A to iron folic acid tablet on hemoglobin level in pregnant women

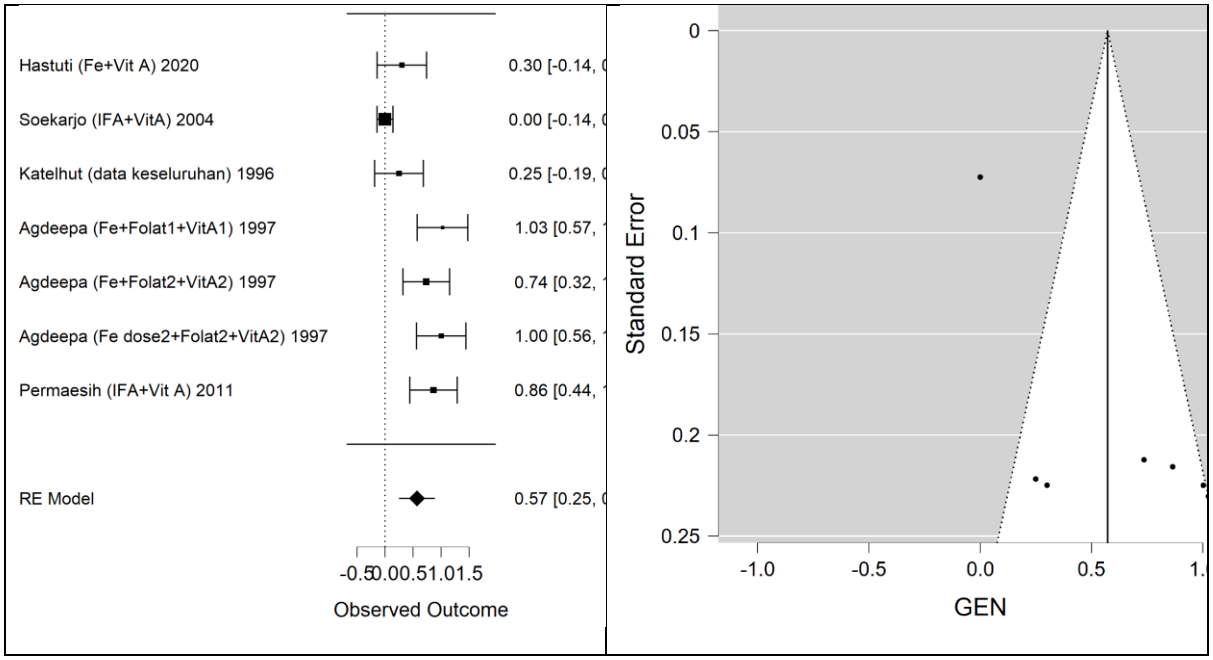

Figure 9b. Meta-analysis result of the effect of adding vitamin A to iron folic acid tablet on hemoglobin level in adolescent groups

7. Effects of iron folic acid tablet consumption on pregnancy output

There are not as many studies on the effects of iron folic acid tablet consumption during pregnancy on pregnancy outcome in Indonesia compared to studies on compliance of iron folic acid tablet consumption in relation to hemoglobin levels or anemia. Meanwhile, studies on the effect of iron folic acid supplement in preventing stunting in children under five are still very rare, so it is insufficient for a meta-analysis. So far, the dose of iron folic acid supplement in Indonesia has followed the recommendations of the World Health Organization (WHO) for areas with a high prevalence of anemia (> 40%), namely iron tablets at a dose of 60 mg Fe and 400 mcg of folic acid. Most of the studies that studied the effect of iron supplement on pregnancy outcome was used preparations containing 60 mg of Fe and 250 mcg of folic acid compared to Fe, folic acid plus other micronutrients such as vitamin A and Zn. Until this paper was written, the Universitas Airlangga/ TPA2AK team had not yet found a published study on the effect of iron supplement on pregnancy outcome using preparations of 60 mg Fe and 400 mcg of folic acid which met the quality requirements for inclusion in this meta-analysis study.

a. The Effect of Adding Micronutrients to Supplements Containing Iron on the Average Birth Weight

There were 9 studies that analysed the effect on birth weight, consist of 8 randomized controlled trial (RCT) studies and 1 quasi-experimental study [68-79]. Four of the studies provided a supplement intervention containing iron and folic acid plus various kinds of micronutrients in one formula, known as the multiple micronutrient formula (MMN), and iron folic acid tablet formula as a control. That four studies were Sunawang et al (2009), SUMMIT (2008), Sumarmi et al (2016), and Widasari et al (2019). The MMN formula used in the study was a formula from the United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP), which contains 15 kinds of vitamins and minerals.

Table 2. The content of micronutrients in the MMN formula from UNIMMAP

No	Micronutrient	Chemical Forms	Content
1.	Vitamin A	Retinol palmitate	800 µg
2.	Vitamin D	5 mcg cholecalciferol	200 IU
3.	Vitamin E	Alpha tocopheryl acetate	10 mg
4.	Vitamin C	Ascorbic acid	70 mg
5.	Vitamin B1	Thiamin hydrochloride	1,4 mg
6.	Vitamin B2	Riboflavin	1,4 mg
7.	Vitamin B3	Niacinamide	18 mg
8.	Vitamin B6	Pyridoxine hydrochloride	1,9 mg
9.	Vitamin B12	Cyanocobalamine	2,6 mcg
10.	Folic acid	Folic acid	400 mcg
11	Iron (Fe)	Iron sulfate	30 mg

12.	Seng (Zn)	Zinc oxide	15 mg
13.	Copper (Cu)	Copper oxide	2 mg
14.	Selenium (Se)	Sodium selenite	65 mcg
15.	Iodium (I)	Potassium Iodide	150 mcg

Sourcer: WHO, 2020 & MMS-TAG, 2020 [67,68]

There were 2 studies that add a single micronutrient, namely Vitamin A (Muslimatun et al, 2002); or adding zinc (Zn) to iron tablet (Hakimah, 2004), while the other two studies provided intervention with moringa flour or leaf extract (Yusnidar et al, 2020; Nadimin et al, 2020). Meanwhile, one quasi-experimental study examined the impact of iron supplementation compared to those without iron supplementation (Achadi, 1995). Therefore, a meta-analysis could only be carried out in 4 studies that analyse the effects of MMN vs. iron folic acid tablet (Figure 10).

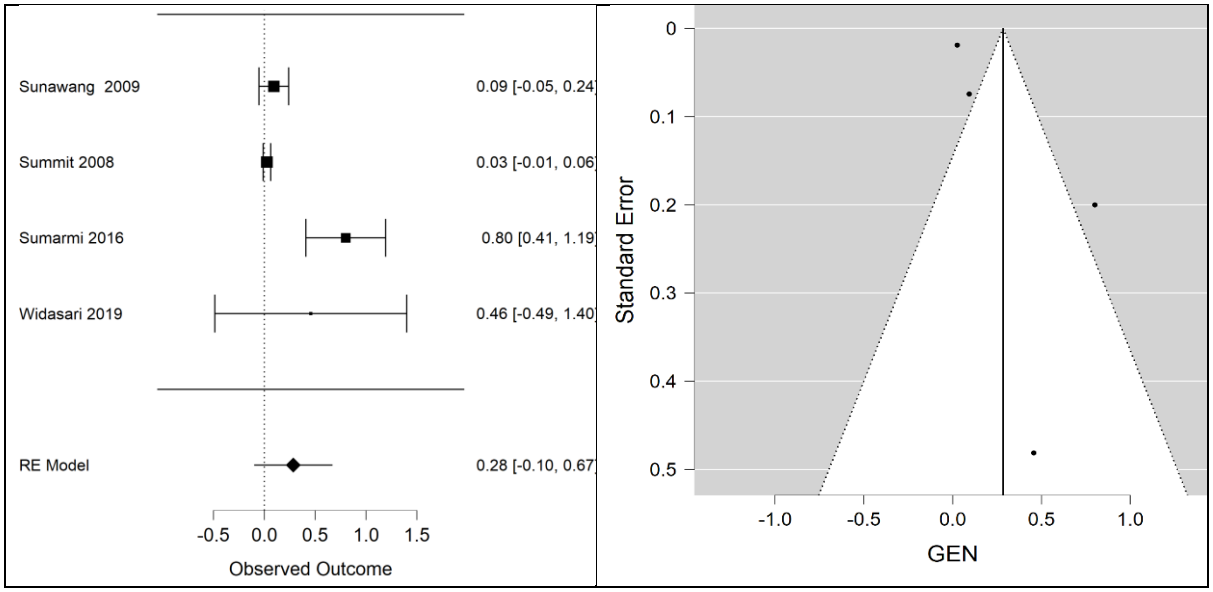

Figure 10. Meta-analysis result of the effects of MMN versus IFA (Iron Folic Acid) on the difference in mean standardized birth weight (standardized mean difference)

Meta-analysis of the effect of MMN on mean birth weight compared to iron folic acid tablet showed a small and insignificant total effect size (Standardized Mean Difference = 0.28; CI -0.10 to 0.67, p = 0.14). However, these results have a fairly large publication bias, so that many similar studies in Indonesia are still needed to ascertain the effect of MMN compared to iron folic acid tablet on the mean birth weight of infants. In addition, the four studies have large variations due to differences in baseline conditions, including hemoglobin levels, duration of intervention, and starting time. The first two studies, intervention was given during pregnancy (SUMMIT, 2008 and Sunawang, 2009), while the other two studies (Sumarmi et al,

2016 and Widasari et al, 2019), interventions were given since the preconception period. However, this study provides sufficient evidence that MMN intervention can overcome growth retardation in the uterus (*Intra Uterine Growth Retardation*). In addition, there have been many meta-analyses on the effect of MMN on pregnancy outcome from various studies conducted in other countries which prove the superiority of the effect of MMN on pregnancy outcome over IFA.

b. Effects of iron folic acid tablet consumption on the incidence of low birth weight (LBW)

There were eleven (11) studies that discussed LBW as a pregnancy outcome, consisting of 2 RCT studies, 5 Case Control studies, and 4 Cross Sectional studies [69-78]. Since there are only two RCT studies, meta-analysis can only be performed in case control studies and cross sectional studies. Of the 5 case control studies, only 3 were included in the meta-analysis (Figure 11). The results of the meta-analysis showed that poor iron folic acid tablet consumption was associated with an increase in the probability of LBW incidence by 4.62 times (OR 4.62; 95% CI: 2.10-10.28, p <0.001). However all three studies are heterogeneous and publication bias remains still.

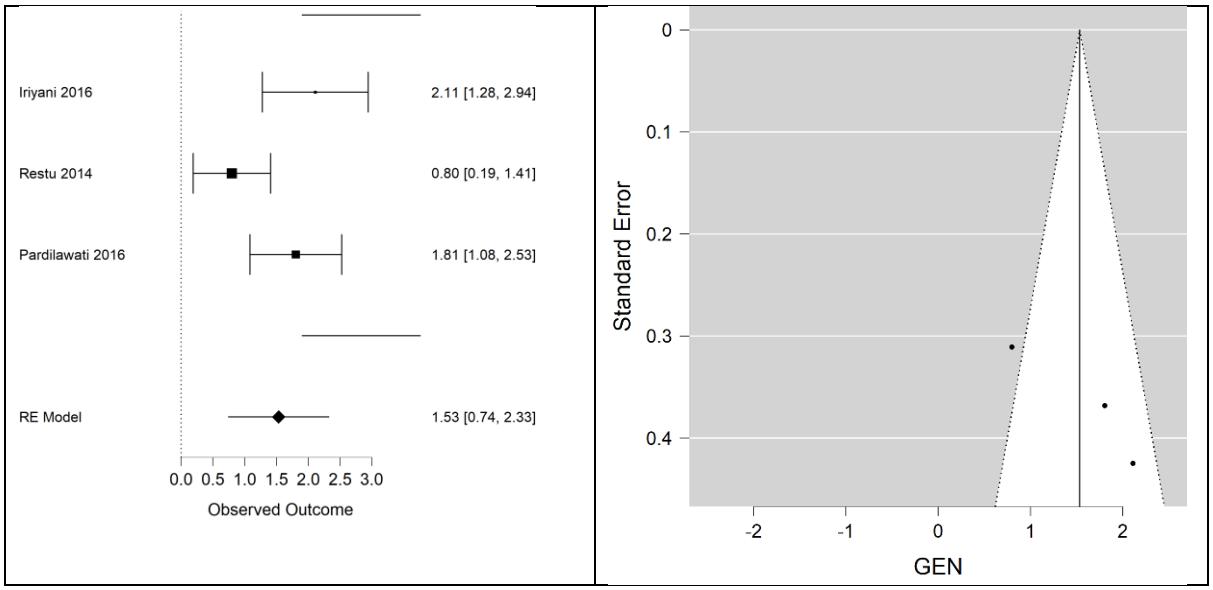

Figure 11. Meta-analysis results of the relationship between iron folic acid tablet intake and low birth weight (Case Control Study)

Meta-analysis of 4 cross-sectional studies showed that poor consumption of iron folic acid tablets was associated with a significant increase in the probability of LBW by 1.38 times (OR 1.38; 95% CI: 1.21-1.57, p <0.001) (Figure 12).

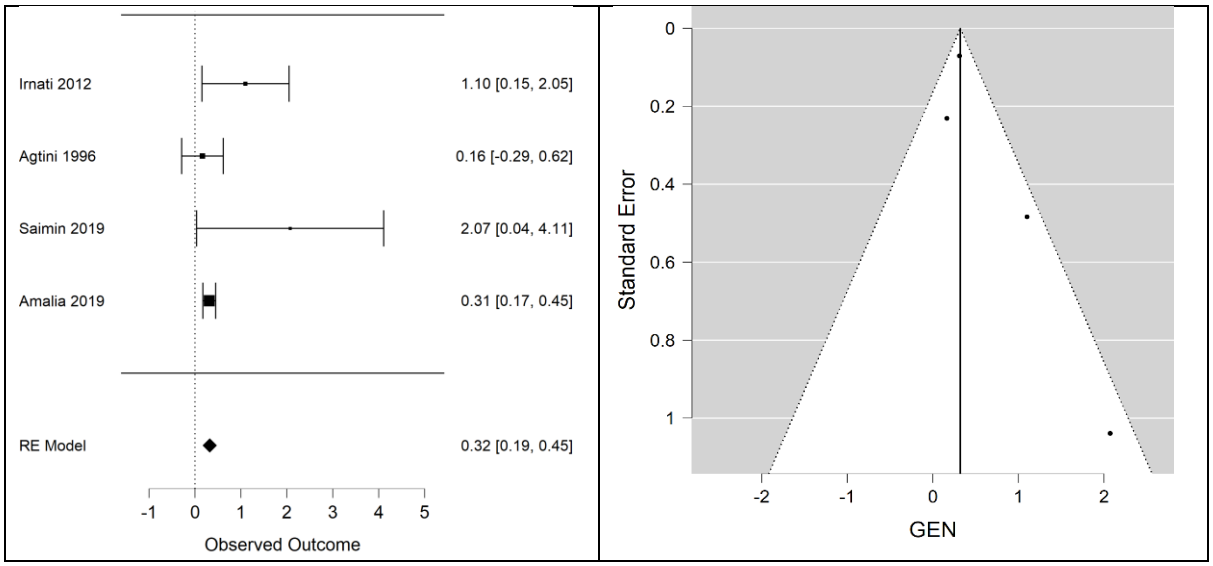

Figure 12. Meta-analysis result of the relationship between IFA consumption and low birth weight (Cross Sectional Study)

There were 2 RCT studies that report the effects of MMN consumption on LBW incidence, i.e., SUMMIT Study (2008) in Lombok and Sumarmi et al (2016). The SUMMIT study reported that MMN supplementation reduced the risk of LBW by 14% (RR = 0.86; 95% CI: 0.73-1.01), while Sumarmi's study (2016) in East Java reported that no babies were born LBW in 56 mothers who were given MMN, while there were 9 LBW babies from 52 mothers who were given IFA.

c. Effects of MMN on Average Birth Length

Meta-analysis of 3 RCT studies measuring outcome of birth length showed that the effect of MMN compared to IFA on birth length was moderate [71,73,75], but not significant with a standardized mean difference of 0.47 (95% CI: -0.09 - 1.03, p = 0.10) (Figure 13). The three studies were not heterogeneous and there was still publication bias. Mean difference analysis was also not significant (MD = 0.98 cm; 95% CI = -0.19 - 2.18, p = 0.10).

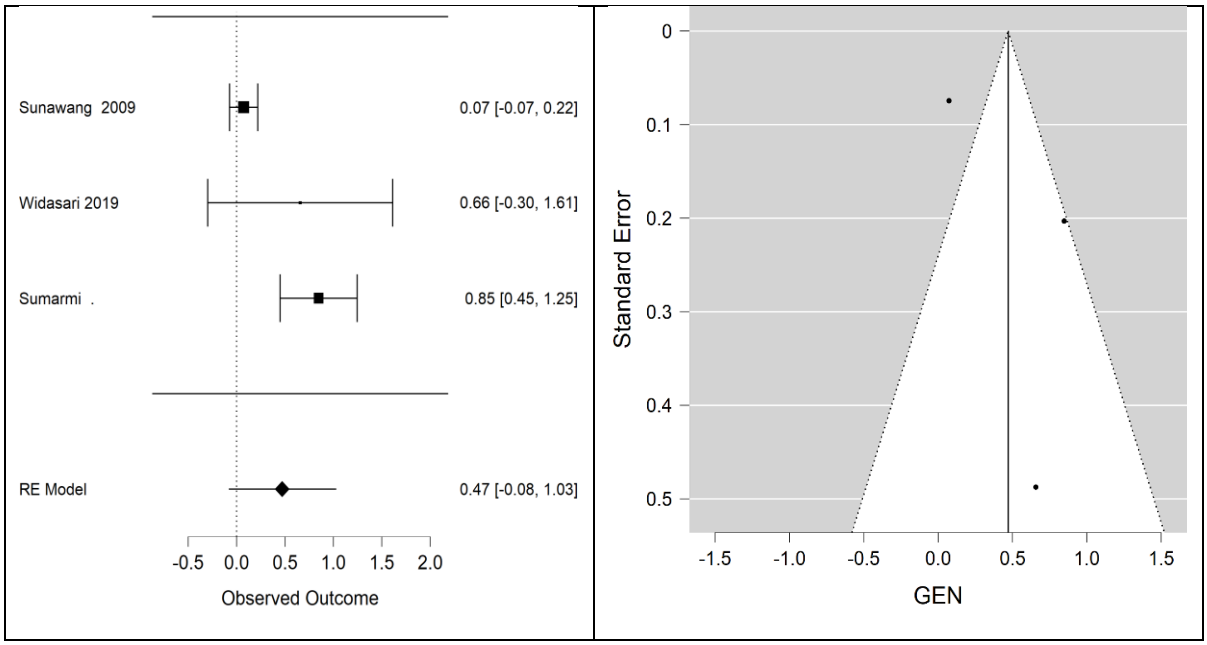

Figure 13. Meta-analysis results of the impact of MMN vs. IFA on the difference in birth length (standardized mean difference)

d. The Effects of MMN Consumption on the Incidence of Neonatal Stunting

There were only 2 studies reported the effects of MMN consumption on the incidence of neonatal stunting, i.e., Sumarmi (2018) and Widasari (2019) study [74,75]. The Sumarmi study proved that MMN supplementation increased the probability of babies born with a body length $\geq$ 48 cm by 5 times compared to iron folic acid supplementation (OR = 5.1; 95% CI: 1.84-14.18, p <0.001). Meanwhile, the Widasari study (2019) proved that there was a 27% reduction in the risk of neonatal stunting, but it was not significant (p = 0.5).

e. Effects of MMN Consumption on Premature Birth Incidence

There were 3 RCT studies that report the effects of MMN consumption on the incidence of preterm birth, namely the SUMMIT study (2008), Sunawang et al (2009) and Sumarmi et al (2016). The SUMMIT study (2008) reported a reduction in the risk of preterm birth among pregnant women who were given MMN by 15% compared to pregnant women who were given IFA, but this reduction was not statistically significant (OR 0.85; 95% CI 0.69–1.05; p = 0.13). Sunawang et al (2009) reported that MMN supplementation compared to IFA had no effect on gestational age (difference in gestational age between MMN and IFA groups = 0.12 weeks (95% CI −0.34 to 0.58; p = 0.61). Sumarmi (2016) also reported a similar result (difference of 1.66 weeks, p = 0.54). Meanwhile, a case-control study reported that the probability of preterm birth increased 5.8 times in pregnant women who did not adhere to take iron folic acid tablet compared to adherent one (OR 5 , 8; 95% CI: 2.89-11.48, p <0.001).

f. Effects of IFA / MMN Consumption on Infant Mortality

There were two studies that discuss infant mortality outcomes, i.e. SUMMIT (2008) with RCT design and Titaley et al (2009) study which analysed secondary data from the Indonesian Demographic and Health Survey (IDHS). Titaley's study showed that the risk of neonatal mortality decreased significantly in mothers who received IFA during pregnancy (HR 0.53; 95% CI 0.36-0.77). In the other hand, the SUMMIT study in Lombok provides evidence that MMN supplementation can reduce early infant mortality by 18% compared to IFA. The infant mortality rate among mothers who received MMN supplements was 35.5 per 1000 live births, while the infant mortality rate for mothers who received IFA was 43 per 1000 live births (RR 0.82, 95% CI 0 · 70–0 95, p = 0 010).

CONCLUSION

1. The adherence of iron tablet consumption in pregnant women was higher than adherence in adolescent girls. Several factors that influence the adherance of pregnant women that mostly found in various studies in Indonesia were pregnant women knowledge about anemia and the benefits of iron tablets and family support, especially husbands and parents. Meanwhile, adherence of adolescent girls was most influenced by iron supplement products, taste and side effects, the role of teachers in the classroom, and the availability of monitoring tools.
2. Educational interventions using diverse media such as flipcharts, short message (SMS) reminders, booklets, and personal counselling can increase compliance to take iron folic acid tablets. However, it should be remembered that adherence is measured in a research framework, where various systematic efforts are made to improve adherence. Meanwhile, the effectiveness of education by program cannot be concluded because there was no study on the effectiveness of educational programs in this meta-analysis study.

3. Consumption of fruits or vegetables, especially guava, beet, papaya and a combination of spinach and honey juice, together with iron folic acid tablet have a profound and significant effect on increasing hemoglobin levels. However, although fruit and vegetable consumption have a positive effect in increasing hemoglobin levels, it has not been able to prevent anemia.

4. The addition of other micronutrients, such as vitamin C and vitamin A, and Zn, which accompany iron folic acid tablet consumption, have a positive effect on the increase in

hemoglobin levels in pregnant women and adolescent girls. The addition of vitamin C has a greater effect on pregnant women than in adolescent girls. On the other hand, the addition of vitamin A along with iron folic acid tablet consumption has a greater effect on the increase in hemoglobin levels in adolescent girls than in pregnant women.

5. Most of the studies that observed the effect of IFA on pregnancy outcome using preparations containing 60 mg Fe and 250 mcg folic acid as controls, compared to the iron formula, folic acid plus other micronutrients or called multiple micronutrients (MMN). Meta-analysis of the MMN effect on mean birth weight, LBW and birth length showed a small to moderate positive effect but not significant. However, these results cannot be fully concluded, because there was still a considerable publication bias due to the small number of studies in Indonesia (there were only 4 studies that meet the requirements). In addition, the other four studies had large variations due to differences in baseline conditions, including hemoglobin levels, duration of intervention, and initiation of intervention.

6. The effect of iron supplement intervention on prematurity and neonatal mortality cannot be enter to meta-analysis because the number of studies was insufficient. However, there were 2 studies which prove that giving MMN to pregnant women can reduce the risk of preterm birth by 15%, whereas giving MMN before pregnancy gives 5.8 times to deliver *full term* baby.
7. Based on the evidence and new WHO recommendations, countries have started exploring the use of MMN formulations from UNIMMAP which contain 15 different vitamins and minerals. This is reinforced by the publication in the latest Lancet Series in March 2021 which describe MMN (Multiple Micronutrient Supplement) supplements or often abbreviated as MMS are important to prevent adverse pregnancy conditions and pregnancy outcomes. Some sources use the terminology Multiple Micronutrient Supplement (MMS) to refer to this UNIMMAP formula. Thus, the MMN and MMS referred to the same thing.

RECOMMENDATION

1. To increase compliance of IFA tablet intake among pregnant women, the most potential targets to be worked on are husbands and parents. It is necessary to encourage a balanced role at home so that pregnant women have a companion in ensuring that iron tablets are properly consumed by pregnant women. Husband's role is not only decision makers or breadwinners, but also an ideal partner for pregnant women in the household to remind

pregnant woman to take iron tablet in every day basis. Optimizing the role of your husband can also be done by reviving the "*Suami Siaga"* movement. The "*Suami Siaga"* movement has been carried out before, but this movement is no longer heard, so it is necessary to mobilize potential resources that can support the movement. In addition, it can also be developed a new innovation such as "*AYAH TTD CEGAH ANEMIA*" movement which is also relevant to become a support program for anemia control programs in pregnant women. Aside from that, health workers can provide an education to increase the husband's insight about the benefits of consuming iron folic acid tablets and the importance of balanced nutrition, as well as the role of nutrients for fetal growth and development during pregnancy. Educational methods can be done through various social media channels. The purpose of this movement is to ensure that the husband can provide positive support, such as motivating wife to consume balanced nutritious foods and iron folic acid tablet throughout pregnancy, becoming a manager in the provision of iron folic acid tablet, establishing good communication between families, strengthening mothers to always consume iron folic acid tablet apart from its side effects, and balanced nutritious food so that all family members can support the movement to prevent anemia by adhere iron folic acid tablets consumption in a movement that is carried out simultaneously in all provinces in Indonesia.

2. To increase compliance of taking iron folic acid tablet among adolescent girls, it is necessary to change the iron supplement formula to be more fun for young women, such as changing the iron tablet packaging to be more attractive, and/or equipped with information on the benefits and how to drink. It is also necessary to do an iron tablet campaign using female teenage figures who are widely known by the community (public figures) or teenage influencers for Communicate, Inform and Educate the importance of iron tablet consumption for teenagers. Adolescents can also form a community to prevent anemia by consuming iron tablets, for example "*Kelompok Pendukung-TTD* or *KP-TTD Remantri*"

3. At school level, there's a need to increase the teacher's role as a motivator for students to take iron folic acid tablets. It is also possible to do a "*taking iron tablet together at class"* movement as a routine activity for students every Monday morning or any certain days within the framework of School's Health Clinic (UKS) activities. Optimizing the UKS program is necessary to also involving Public Health Center sector, schools, parents, teachers, religious leaders (TOGA) and public figures (TOMA) with an approach according to age groups.

4. Based on the meta-analysis results, it is suggested to take iron folic acid tablet together with other micronutrients which act as an enhancer to optimize the elevation of Hb levels. This can be obtained by suggesting consuming iron tablets together with taking fruit or fruit juices rich in vitamin C such as guava, papaya, or consuming MMN containing vitamin C and vitamin A. In other words, it is necessary to think about multi-micro nutrients to get better effect at increasing Hb.

5. If one type of micronutrients is added in the iron supplement administration, pregnant women have actually consumed multi-micro nutrients (MMN), because MMN is based on a formula consisting of at least 3 micronutrients. Taking into account the various results of the MMN efficacy study on pregnancy outcomes as well as WHO recommendations regarding the use of MMN, it is necessary to implement further studies to obtain evidence of the possible impacts that arise in switching IFA to MMN. In this context, the MMN recommended by WHO is a formula containing 15 different vitamins and minerals from UNIMMAP [67,68,93].

6. From a program perspective, if the focus is on overcoming the problem of anemia, iron tablets still can be used, but it needs to be accompanied by a management program and other efforts to increase its effectiveness. This is in accordance with WHO recommendations which stated areas with a high prevalence of anemia (>40%), 60 mg Fe & 400 mcg folic acid preparations are used. However, to get a conclusion on the effectiveness of iron supplement on the quality of pregnancy outcomes, evidence is still needed from a research on program implementation with a robust and rigorous research design, by comparing the MMN formula preparations from UNIMMAP that have been used in several districts assisted by UNICEF and other districts that have used it. Pregnancy outcomes that need to be observed in accordance with the latest WHO recommendations (2020) are outcomes in babies including low birth weight (LBW), small for gestational age (SGA) and prematurity, as parameters that become initial modalities in preventing stunting in children under-five. In addition, neonatal infections, congenital disorders and neonatal mortality are also present. Likewise, the effect on maternal outcomes in the form of pregnancy complications such as preeclampsia, postpartum hemorrhage, and infection which is the biggest cause of maternal mortality, still needs more clear evidence.

7. It is necessary to study the effectiveness of the iron supplement program nationally, seen from the aspect of compliance, national prevalence on how much iron supplement can be received by pregnant women and adolescent girls. In addition, it is necessary to consider the iron supplement efficacy study in adolescent girls, which compares the iron folic acid supplement (IFA) formula with the multi micronutrients (MMN) formula, as well as effectiveness and implementation studies to improve iron supplement programs which aims to see the management aspects of the iron supplement program management for adolescent girls, related to the health benefits obtained against the costs incurred for program implementation (starting from the cost of procurement, distribution to consumption) or cost benefit analysis and cost benefit effectiveness.

8. The iron folic acid supplement program for adolescent girls still needs to improve its program management aspects, from the distribution and storage chain, recording and reporting systems, program monitoring to compliance aspects. Strengthening the School's Health Clinic (UKS) program through partnerships with universities and community institutions can also be done. Another weakness of the anemia control program for adolescent girls is that the program targets are still limited at school, while other girls outside of school have not had access to the iron supplement program. For this reason, it is necessary to think about distribution channels that can reach larger group, through the channels of social organizations and other non-governmental organizations.

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Abbreviation

IFA	Iron Folic Acid
WHO	World Health Organization
MMN	Multiple Micro Nutrient
MMS	Multiple Micronutrient Suplement
RISKESDAS	*Riset Kesehatan Dasar* / Basic Health Survey
RCT	Randomized Control Trial
IU	Internnational Unit
UNIMMAP	United Nations International Multiple Micronutrient Antenatal Preparation

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