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The effect of selenium and multiple micronutrient administration during periconception period on the level of malondialdehyde[☆]

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Abstract
Objective: This study aimed to prove the effect of Selenium during periconception to the level of Malodialdehyde in pregnancy.
Methods: This study was double blind, randomised, control community based trial design. The intervention group (10 periconception women) received Selenium in Multimicronutrient (MMN), while the control group (22 periconception women) given capsules containing Iron and Folic Acid. During preconceptional period, the capsules was given once a week, while in pregnant women was once a day. At the 12th and 20th weeks of pregnancy, selenium and MDA were measured. Statistical analysis using independent *T*-test, Paired *T*-Test and PLS analysis.
Results: At the 12th weeks of pregnancy the level of MDA in Multimicronutrient group was 121.2 ng/mL and IFA group was 1436 ng/mL, and at the 20th weeks in MMN group was 108.4 ng/Ml and IFA group was 199.6 ng/mL. There was a no significant difference between MDA in two groups ($p = 0.424$) at 12th week, but at 20th weeks MMN group had a significantly lower MDA levels ($p = 0.006$) than IFA group.
Conclusion: The administration of selenium in MMN preparations since the preconception period has a better effect in reducing MDA levels compared to the IFA group.

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Introduction

Preeclampsia is still the main cause of mortility and morbidity among mothers and their babies. In Indonesia, preeclampsia is the second most frequent cause of mother mortality. About 16% of mother mortality cases are due to preeclampsia.[1,2]

The mechanism of micro nutrient role in preventing preeclampsia has not been completely identified, but it can be explained through antioxidant and oxidative stress, as nutrition can balance and prevent free radicals which cause oxidative stress during pregnancy.[3] Established preeclampsia is associated with increased concentrations of oxidative stress markers including lipid peroxidation products, and a reduction in antioxidant concentrations.[4]

Efforts to prevent preeclampsia have been done through intervention using antioxidant micronutrient, because there is an evidence of the involvement of placental oxidase. Micronutrient substances are strongly correlated with complications during pregnancy such as preeclampsia. Oxidative stress plays a role in such incidence. In some journals, it is claimed that the intervention is not effective, and there is even a potentiality to be harmful.[5,6] Therefore, an intervention is started with the use of Selenium. Selenium is an essential micromineral component of Glutathione peroxidase enzyme. This enzyme, together with superoxide dismutase (SOD) catalystand vitamin E have a strong antioxidant power to survive oxidative damage by free radicals. Selenium is a part of antioxidant enzyme that protects cells and lipid membrane from oxidative damage.[7]

The role of Selenium in preventing preeclampsia has been proved in some researches.[8,9] It is evident that the decrease of Selenium level results in oxidative stress in the placenta, leading to preeclampsia symptoms.[10] The relationship between Se status and preeclampsia incidence is shown in some researches in 45 countries.[11] Se supplementation among women in China can prevent hypertension and oedema during pregnancy.[12] An interesting study on animals tries to show that diet without Se results in some symptoms like preeclampsia, including the increase of blood pressure, proteinuria, and oxidative stress in the placenta compared to the use of normal Se.[13]

The role of selenium intervention in preventing preeclampsia is related to MDA level. A review conducted by Raijmakers et al.[14] shows that Malondiadehyde (MDA) is the main oxidative stress biomarker found in the circulation of pre-eclampsia women where a number of studies have reported that this lipid peroxide product increases in preeclampsia pregnancies.

A 1987 and 2005 review and a recent systematic review of the literature between 1987 and 2007 concluded that overall there was an increase in MDA in women with preeclampsia.[4] So far, research on selenium supplementation with other multimicronutrients since the preconception period which has influenced MDA levels in pregnant women is still not widely practiced. The writers have not found any research on selenium intervention with Multiple Micronutrient preparation. It is expected that the combination of selenium and other antioxidant such as vitamin A, C, and E, and antioxidant minerals such as ferrum, zinc, and copper can provide a synergic effect against free radicals and prevent placental oxidative stress, and decrease MDA level, leading to the prevention of endothelium tissue that can increase the risk of molecular preeclampsia.

It is then necessary to conduct a research about the effect of Selenium intervention in (Multiple Micronutrient/MMN) preparation since preconception period on the levels of MDA to prevent oxidative strees in pregnancy. This research aimed to analyse the level of MDA before and after the administration of Multimicronutrient supplement containing selenium and to compare the MDA level at the 12th and 20th weeks of pregnancy in the intervention and control groups.

Methods

Design

The research will be conducted in three subdistricts in Banggai regency. These three subdistricts are selected purposively as the representation of Banggai regency area based on some considerations. First, the rate of preeclampsia is high in these three areas. Second, the three locations are accessible, making it possible for monitoring and controlling the intervention. Third, the three subdistricts are similar in terms of the socioeconomic aspect. Finally, people mobility in the three subdistricts is relatively low.

This study can be considered a true experimental research using the double blind community-based trial design. It can also be regarded as an efficacy study aimed to analyse the advantage or benefit of an intervention under a tight control.[15] The scheme description is as follows:

Population and study setting

The number of samples is determined with a 90% power to detect 386 differences of sFlt-1 concentration, with type I error in $\alpha = 0.05$ on one side, standard deviation (SD) 772 (based on the study of Mousavi M.[16] There are 34 preconcentional mothers in each group. The research population includes preconceptional mothers who register in the programme of Praconception Integrated Service Centre. They are from three subdistricts in Banggai regency. The samples are eligible respondents based on some inclusion criteria: praconceptional mothers, do not have previous pregnancy, married, aged 18–35 years old, plan to be pregnant in less than one year, and agree to participate in the research by signing an informed consent. The exclusion criteria are preconceptional mothers with hyperglycemia, ddabetes mellitus, kidney failure, hypertension, and tuberculosis; not a permanent citizen in the areas (stay duration < 6 months), not living with husband, twin pregnancy, obesity (IMT > 30), severe anaemia (<7 g/l), upper arm circumference < 23.5 cm, positive proteinuria (++), six-month participation in the intervention programme but not getting pregnant, have been married > 6 years but never get pregnant.

A block IV randomisation results in a group receiving selenium and Multimicronutrient, and a control group receiving programme capsules containing Iron and Folic Acid. The MMN capsules containing Selenium and other Multimicronutrient will be given once a week when the mothers are not pregnant, and once a day during pregnancy. The intervention will be stopped when after six-month intervention, the

Table 1 The composition of iron folic acid and multiple micronutrient supplements.

Ingredient	Preconception (weekly)		RDA for non-pregnant women
	IFA	MMN	
Vitamin A, RE		800	700
Vitamin B12, μg		2.6	2.4
Vitamin B6, mg		1.9	1.3
Riboflavin (B2), mg		1.4	15
Vitamin C, mg		70	75
Vitamin D, IU		10	15
Vitamin E, mg		10	15
Zinc, mg		15	8
Iron, mg	600	30	18
Niacin, mg		18	14
Selenium μg		65	55
Copper, mg		2	900 mcg/day
Folate, μg	400	400	400
Iodine, μg		150	150

mothers do not get pregnant so that the respondents will be considered dropped out (Table 1).

The distribution of intervention and control capsules to mothers will be conducted starting from the researcher to subdistrict coordinators, who will then distribute the capsules to village midwives. These village health workers will distribute the capsules among the cadres of integrated service centres in each village. Respondents will be visited once in a week to distribute the MMN capsules as well as to control the adherence in consuming the MMN capsules. During the research, the mothers will not be allowed to consume vitamin and minerals from other sources. Any violation of this requirement will result in the cancellation of respondents' participation in the study.

Data collection

Types and time of data collection can be seen in Table 2.

Pregnant mothers will be required to consume one supplement capsule before night sleeping every day. The cadre will distribute the supplements every fortnight, and at the same time, the cadre will monitor the consumption. In addition, the cadre will also record side effects and any pain felt by the mothers. Furthermore, the pregnant mothers will have blood pressure examination, proteinuria assessment, and anthropometric measurement. Their blood samples will also be taken to determine the levels of hb, glucose, and MDA at the first stage. At the 12th and 20th weeks of pregnancy, blood sample examination will be conducted to

Table 2 Data collection and measurements.

Measurements	Preconception	Pregnancy	
		12 weeks	20 weeks
Demographics, SES status	√		
OBGYN history	√		
Environment sanitation	√		
Exposure to pollutans	√		
Access to health and nutrition information	√		
Morbidity	√		
Haematological measures	√	√	√
Anthropometry	√	√	√
Food recall 24 h	√	√	√
Food frequency questionnaire	√	√	√
Haemoglobin	√	√	√
Blood pressure	√	√	√
Urine protein	√	√	√
Urine glucose	√	√	√
Urin PH	√	√	√
Blood MDA	√	√	√
Supplement consumption	√	√	√
Side effects	√	√	√

measure MDA level at the second stage. The pregnant mothers will also have blood pressure measurement every month, and proteinuria examination at the 20th week of pregnancy. After the samples are taken for examination, the administration of Multiple Micronutrient will be continued until the time close to baby delivery. The examination of MDA level will be conducted in the Clinical Pathology Laboratory of Dr. Soetomo hospital. The pregnancy examination will be conducted by village midwives at the Intergated Service Centre or Village Health Centre. Pregnant mothers experiencing complications will be referred to an *Obstetrics and Gynecology* specialist.

Result

The results of laboratory analysis showed the average value of MMN group MDA as well as Folate Iron group increased at 12 weeks as shown in Fig. 1. In the MMN group, the mean sect of MDA at preconception time was 112.8 ng/mL slightly lower than Iron Folit Acid group of 120.8 ng/mL. Furthermore, at 12 weeks of gestation the mean score of MDA in the MMN group increased to 121.2 ng/mL ($p = 0.681$) so in the Iron Folit Acid group increased to 143.6 ng/mL ($p = 0.636$). The mean value of the MDA was then decreased to 108.4 ng/mL in MMN group at 20th week of pregnancy, and the Folate Iron group increased to 199.6 ng/mL.

Fig. 2 shows that at week 12 there was an increase of MDA in both groups, i.e. 8.4 points in MMN group and 22.8 points in Iron Folit Acid group. Furthermore, at week 12–20th week of pregnancy, in MMN group there was a decrease of MDA of 12.8 points ($p = 0.636$), and in Iron Folit Acid group there was an increase of MDA by 56 points ($p = 0.030$). Thus, a greater decrease in MDA occurred in the MMN group than in the Folate Iron group as it entered the 20th week of pregnancy.

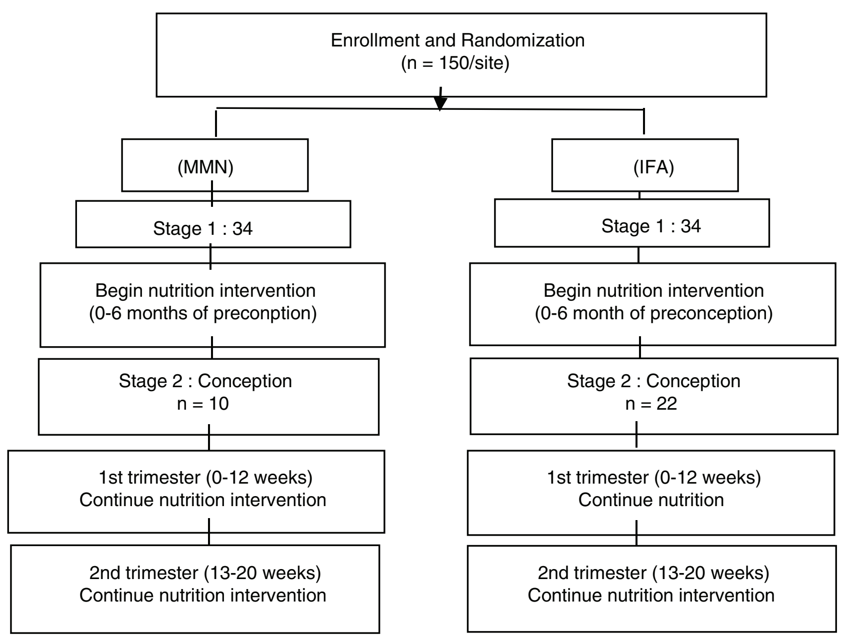

Figure 1 Consort diagram (subject numbers are for each independent site).

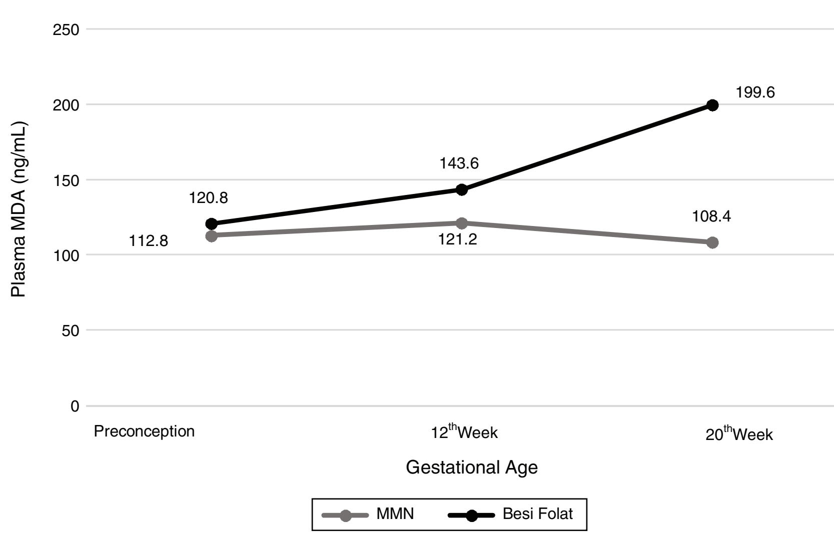

Figure 2 Comparison of mean values of MDA in preconceptions, week 12 and week 20 in the Iron Folit Acid group and MMN group.

The statistical analysis showed that the mean difference of the mean MDA for the two groups at week 12 was −22.38 with p value = 0.424, whereas at week 20, the mean difference was −91.3 p value (0.006). There were significant differences in either group at week 20.

Discussion

The results of the study in Fig. 2 show that at 12 weeks of gestation an increase in the MDA in both groups was 121.2 ng/mL respectively in the MMN group and 143.6 ng/mL in the Folate Iron group. In both groups there was no significant difference with the value of $p = 0.424$.

The increase in MDA levels in this study is in line with the results of Lucca L's study[16] which showed that in pregnancy there was an increase in MDA levels, despite the intervention of antioxidant supplements since the beginning of pregnancy. This condition is associated with high metabolic needs and increased oxygen demand in the tissues resulting in increased production of reactive oxygen species.[16] Thus the efficacy of selenium supplementation in MMN preparation given since preconception has a better effect than the Iron Folate group in suppressing the rate increase of MDA levels at week 12 of pregnancy.

Furthermore, at 20th week of gestation the decrease in MDA level occurred in MMN group, i.e. 108.4 ng/mL in the MMN group and on the other hand, in the Iron Folate group there was an increase in MDA levels (199.6 ng/mL). In the 20th week of pregnancy there was significant difference between the two groups with $p = 0.006$.

Conclusion

Thus, it can be concluded that the efficacy of selenium supplementation in MMN preparations given since preconception time is more effective in reducing the MDA level at 20 weeks of pregnancy than in the group given the Iron Folit Acid supplement. This condition is very good in preventing oxidative stress in pregnancy and preeclampsia early.

Conflict of interest

The authors declare no conflict of interest.

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