



## The Effects of Combined Omega-3 and Vitamin E Supplementation on Preeclampsia Cases in Hasan Sadikin Hospital Bandung

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**Abstract:** Etiology and pathogenesis of preeclampsia syndrome have not been fully understood, although the theory of stress oxidative inducing endothelial injury has been studied for many years and it has been recognized to play a key role in preeclampsia development. Polyunsaturated fatty acid (PUFA) omega-3 shows beneficial effect in cardiovascular remodelling for women with hypertension. In addition, low intake of vitamin E has been found as a predictor of preeclampsia. Observational data reveals that omega-3 supplementation without vitamin E has no significant effect on vascular endothel. This study is an interventional, randomized control trial with single blind technique. It is conducted by comparing pregnancy induced hypertension cases that are divided into two groups with different treatments. One group was given antihypertension medicine, omega-3 and vitamin E supplements while the other was only given antihypertension medicine. This study aims to determine the effect of the supplementation of combined omega-3 and vitamin E in preeclampsia development. The study was conducted through 36 females with gestational hypertension from January to April 2014 at Hasan Sadikin Hospital with its network-hospitals. Blood pressure and protein urine examination were assessed before and after intervention. The result shows that on the interventional group, only 4 subjects had a progression into preeclampsia, whereas on the non-interventional group, 11 subjects (61.11 %) were found (22.2 % vs 61.11 %) with p value 0.015 ( $p < 0.05$ ). It is concluded that the supplementation of combined omega-3 with vitamin E could prevent the development of preeclampsia.

**Keyword** (Omega-3, pregnancy induced hypertension (PIH), stress oxidative, vitamin E).

### Introduction:

Pregnancy hypertension is a complication that may occur in 5-10 % pregnancies and one of triad causes of death besides bleeding and infection. The World Health Organization (WHO) 10-years data, from 1990 to 2000, states an increase in preeclampsia and eclampsia cases in both developing and developed countries. In developing countries, the percentage of the case increased from 0.5% to 2.3 % whereas in developed countries from 0.1% to 0.8%. Moreover, pregnancy hypertension cases in Hasan Sadikin Hospital also tend to increase

every year. In 2009, there was 170 gestational hypertension cases which increased to 175 in 2010. Mild preeclampsia increased from 58 in 2009 to 222 cases in 2012; severe preeclampsia increased from 176 in 2009 to 192 cases in 2010 and 242 cases in 2011; whereas eclampsia increased from 54 in 2009 to 64 cases in 2010<sup>1-6</sup>.

The sudden change from normotension to hypertension in pregnancy without proteinuria symptom known as gestational hypertension will develop into preeclampsia in nearly half of the cases. Unfortunately, the etiology and pathogenesis of preeclampsia have not been fully understood. There is some evidence that the diverse manifestations of preeclampsia, including changes in vascular reactivity, vasospasm, and various pathology in some organ systems are caused by pathological changes of the maternal vascular endothelium. Various theories such as immunology, genetic and oxidative stress have been used to explain the etiology of preeclampsia. However, oxidative stress theory is one of the most explorable theory out of the three.<sup>1,7,8</sup>

Oxidative stress is a condition characterized by an imbalanced amount of free radicals and antioxidants associated with the increasing of reactive oxygen and often followed by disturbances of endogenous antioxidant mechanisms. Several recent reports show that the free radicals that induce endothelial cell damage have a possibility to be a contributing factor in pregnancy hypertension. The imbalance between the increase and the decline of the antioxidant status in females with preeclampsia has also been understood. Low levels of antioxidant enzymes such as catalase, glutathione, vitamin A and E can be seen in preeclampsia cases. Lipid peroxidation also has a role in the stress oxidative process. Lipid peroxidation is an oxidative degradation of saturated fatty acids. It involves direct reaction of oxygen and lipid to form lipid peroxide. This is one of the important consequences of free radical formation process. Lipid peroxidation is destructive because it causes a harmful chain reaction.<sup>9,10</sup>

For a long time, maternal nutrition status also has been playing a role in pregnancy hypertension pathophysiology. Dyslipidemia condition in pregnancies increases the risk of preeclampsia. Usually, this is associated with the life style such as using saturated cooking oil or consuming high-cholesterol food. Lifestyle choices, measurement of intake nutrition (antioxidants such as vitamin C, vitamin E, lycopene, selenium, zinc, magnesium, and mitochondrial antioxidant such as nicotinic, Q10 co-enzyme, and melatonin) and other measurement intake such as low-salt diet, omega-3 fatty acid, folic acid, garlic, protein and energy supplementation, or energy limitation for women with obesity as well as the use of other drugs, did not show strong evidence for clinical use.<sup>11,12</sup>

*Polyunsaturated fatty acid* (PUFA) omega-3 shows beneficial effect in cardio-vascular remodelling in women with hypertension. Several research shows that omega-3 has a protective effect in preeclampsia cases but on the other hand some research show the contradictive results. Olafsdottir *et. al.* report the correlation between PUFA omega-3 intake and the reduction of pregnancy hypertension risk. Zhou *et. al.* reported that omega-3 supplementation in mid to late pregnancies did not reduce the risk of preeclampsia.<sup>13-15</sup>

Many studies on vitamin E supplementation as antioxidant have been conducted. Accumulation of supporting evidence since 30 years ago reveals that oxidative stress has a role in the pathogenesis of preeclampsia and observational data shown that low level of vitamin E has become a predictor of preeclampsia. However, some of the research shows a variety and contradictive results. In 1999, a randomized controlled study with 400 IU of vitamin E supplementation starting at the age of 20-weeks pregnancies in women with high risk preeclampsia was conducted. The result of this study shows a decrease of 61% on preeclampsia cases. On the other hand, Mohanty *et. al.* reported that there was no correlation between vitamin E supplementation and preeclampsia risk.<sup>13</sup>

Bruckner *et. al.* reported in their study that the combination between PUFA omega-3 and vitamin E changes the ratio of vasoconstriction - thrombosit aggregation / vasodilatation - thrombosit anti aggregation (TXA2 and endothelin/PGI2 and nitrite oxide) agent, the expression of adhesion molecule (selectin-P and selectin-E) and it directly affects the modulation of radical free interaction between blood component and vascular endothel. Omega-3 fatty-acid will help the production of vasodilatation component and reduce the expression of selectin P and/or selectin E. The lipid that is easily oxidized will be protected by adequate antioxidant.<sup>16</sup>

## Subjects and Method:

This study is an interventional, randomized control trial with single blind. The subject of this study is pregnant women with over 20-weeks of pregnancies, diagnosed with a gestational hypertension and have completed antenatal check-ups at the Hasan Sadikin Hospital or its network hospitals during the period of the study.

### Inclusion criteria:

1. Gestational hypertension
2. Alive fetus in a singleton pregnancy
3. Gestational age over 20 weeks
4. Maternal age < 35 tahun
5. Willingness to participate in this study

Pregnancies with severe hypertension, immunology disorder and vascular diseases are excluded (exclusion criteria) from this study. After the subjects have given their consent, they were grouped using randomized permutation block method. In the treatment group, each subject was given a 300 mg omega-3 fatty acid supplement which consist of 180 mg eikosapentanoic acid, 120 mg dokosa-heksanoic acid, 20 mg vitamin E, and anti-hypertensive drugs (methyl dopa 3x250 mg, titration dose) for a period of 2-months (n=18). In the control group, the subject was given anti-hypertensive drugs only (methyl dopa 3x250 mg), without other supplements.

Statistical analysis was initiated by analyzing the characteristics of two groups, followed by *Chi-Square* test and alternative analysis using *Exact Fisher* method for categorical data. For numerical data, *t* statistical test was used for the data with normal distribution and *Mann whitney* test was used for the data with abnormal distribution. To check the distribution of the data, *Shapiro Wilks* test was conducted (because  $n < 50$ ), then the data was analyzed again using *Chi-Square* test and *Exact Fisher* alternative test. Statistical significance test result was determined by the value of  $P < 0.05$ . The data from this study was recorded in a specific form and has been analyzed using *SPSS* ver 20.0 software for *Windows*.

## Results:

The study was conducted to 36 women with pregnancy induced hypertension from January to April 2014 at Hasan Sadikin Hospital and its network-hospitals such as Astana Anyar hospital, Sumedang hospital, Cianjur hospital, and some private midwife around Hasan Sadikin Hospital. The subjects were divided into two groups, treatment group which is given omega-3 and vitamin E supplementation and control group which were not given other supplements. Maternal age, parity, gestational age, and body mass index (BMI) data were collected from the two groups. Every two-weeks, the blood pressure was measured and the urine was collected to examine its protein level. During this study, one subject was excluded due to the progress of the gestation hypertension into severe preeclampsia which occurred in week-4, resulting in the termination of the pregnancy.

**Table 1. Study Subject Characteristic**

Characteristics	Pregnant women with gestational hypertension or mild preeclampsia				p Value
	Treatment group		Control Group		
	n	%	N	%	
Age					<b>0.757</b>
a. < 20 years	1	5.6	1	5.6	
b. 20-35 years	17	94.4	17	94.4	
Education					<b>0.847</b>
a. Elementary School	6	27.8	7	38.9	
b. Junior High School	7	38.9	7	38.9	
c. Senior High School	4	22.2	3	16.7	
d. University	2	11.1	1	5.6	

Body Mass Index (BMI)					<b>0.203</b>
a. Underweight	1	5.6	0	0	
b. Normoweight	5	27.8	11	61.1	
c. Overweight	8	44.4	5	27.8	
d. Obese	4	22.2	2	11.1	
Gestational Age					<b>0.244</b>
a. 20-24 weeks	13	72.2	10	55.6	
b. 24-28 weeks	5	27.8	8	44.4	

For categorical data p value calculate based on *Chi-Square* alternative *Fisher Exact* test. Statistical significance test result is dertermined by the value of  $P < 0.05$ . \*\* symbols show the significance of data.

The significance of the data was not found in age category, education category, BMI category, and gestational age category (because each category has p value  $> 0.05$ ). Therefore, the two study groups have homogeneous characteristic.

**Table 2. The effect of omega-3 and vitamin E combined supplements on preeclampsia case**

Study Subject Group	Gestational hypertension		Mild preeclampsia		Severe preeclampsia		p Value
	n	%	n	%	n	%	
Treatment group	14	77,8	4	22,2	0	0	0.015**
Control group	7	38,9	5	27,8	6	33,3	

For categorical data, p value was calculated based on *Chi-Square* alternative Kolmogorov Smirnov test. Statistical significance test result was dertermined by the value of  $P < 0.05$ . \*\* symbols show the significance of data.

In the treatment group which was given combined omega-3 and vitamin E supplements, there were 4 subjects (22.2%) who developed into mild-preeclampsia and none developed into severe preeclampsia. The other 14 subjects (77.8%) remained in gestational hypertension diagnosis. Meanwhile in the control group, there were 7 subjects (38.9 %) who remained in the gestational hypertension diagnosis and the other 11 subjects (61.11%) developed into preeclampsia cases (5 subjects (27.8%) developed into mild preeclampsia and 6 subjects (33.3%) developed into severe preeclampsia).

Based on the statistical analysis, this study concludes that there is a significant correlation between the combined omega-3 and vitamin E supplementation and preeclampsia cases for those two study groups (the p value is 0.015) therefore it is significant.

## Discussion:

Subject characteristics in this study include maternal age, Body Mass Index (BMI), and gestational age. These characters were selected as they can potentially obscure the validity of this study.

Etiology and pathogenesis of preeclampsia syndrome have not been fully understood. The diverse manifestations of preeclampsia such as vascular reactivity changes, vasospasm, and various pathology in some organ systems lead to a limitation of the subjects of this study in order to prevent bias. The subject was limited to maternal age below 35 years of age to avoid chances that the preeclampsia progression was caused by other pathology.

Oxidative stress is a condition characterized by an imbalance amount of free radicals and antioxidants, associated with the increase of reactive oxygen, and often followed by disturbances of endogenous antioxidant mechanisms. The main resource of free radical synthesis is a placenta, but maternal leukocytes and maternal endothelium are also considered as contributors in the free radical synthesis process. In the recent report, there is a statement that NAD(P)H oxidase in plasental trophoblast also plays a role in the emerging of free radicals in preeclampsia case. Oxidative stress has a high tendency to occur in pregnancies. The increasing mitochondrial

activity in pregnancies most likely would increase the oxidative stress level. Many studies on the increase of oxidative stress have been conducted. Most of these studies were related to preeclampsia condition or fetal growth restriction. Endothelium of pregnant women is the main target of the free radical. The existence of free radical will cause vascular malfunction in pregnant women. The increase in oxidative stress could also cause fetal vascular malfunction.<sup>9,10,17,18</sup>

Lipid peroxidation product is a potential factor for causing maternal vascular endothelial dysfunction. Although it is not directly assessed in the spiral artery, some study results show that the concentration of lipid hydroperoxide, phospholipid, and cholesterol in decidua basalis tissue in women with caesarean section experience were significantly higher than those with normal deliveries. Lipid membran peroxidation can lead to disappearance of PUFAs, the decreasing of membran fluidity, and the increasing of membran permeability for some components such as  $\text{Ca}^{2+}$  ion. Lipid peroxidation could make enzyme and receptor reactivity disappear and also cause the disappearance of membrane secretion function. The continuation of lipid peroxidation reaction can make the membran lose its integrity just like lipid peroxidation in hemolytic process of erythrocytes membrane.<sup>8,19</sup>

Cellular lipid peroxidation strongly depends on PUFAs, vitamin E, and another lipid antioxidant intake. After digested, essential fatty acid is distributed into adipose tissue and other tissue with lipid structure. PUFAs are oxidized faster than the other nutrients. In liver, PUFAs undergo some metabolic process and the 18-carbon essential fatty acids are transformed into 20 to 22 carbon length long-chain PUFAs. The long-chain PUFAs then moved to extrahepatic tissues. The essential fatty acids are important because typically the erythrocytes and mitochondria membrane are fragile in deficiency of essential fatty acid condition. The function of essential fatty acid is as phospholipid integral component for keeping the integrity of intercellular membrane and plasma. Vitamin E is a nutrient resource and has a specific role in some metabolic functions. The function of vitamin E is an antioxidant that prevent the propagation mechanism in radical free reaction on biological membrane. Vitamin E is also a sweeper for peroxy radical and has a role in protecting PUFAs in the biological membrane phospholipid and lipoprotein plasma.<sup>19</sup>

Olafsdottir *et. al.* reported the correlation between PUFAs omega-3 intake and the decreasing of pregnancy hypertension risk while Zhou *et. al.* reported that the supplementation of omega-3 does not reduce the preeclampsia risk. In 1999, a randomized controlled study with 400 IU of vitamin E supplementation starting at the age of 20 weeks of pregnancy in those with high risk preeclampsia was conducted. The results of this study shows a decrease in preeclampsia incidence up to 61%. On the other hand, Mohanty *et. al.* reported that there was no correlation between vitamin E supplementation with the risk of preeclampsia incidence. These showed many contradictions on the PUFAs omega-3 and vitamin E supplementation to prevent of the incidence of preeclampsia.<sup>13-15</sup>

Bruckner *et. al.* reported in their study that omega-3 significantly reduces triglycerides level and VLDL cholesterol (especially if the subject has a high initial triglycerides level). Omega-3 also increases the LDL cholesterol and Apo-B100. This effect is important because the oxidation reaction of LDL from omega-3 supplementation will not disappear for 2 months. The combination of supplementation of vitamin E and omega-3 also prevents these alteration. This data show that the supplementation of omega-3 without vitamin E supplementation is not enough to affect the vascular endothelial.<sup>16</sup>

This study shows that the combined omega-3 and vitamin E supplementation can prevent the incidence of preeclampsia. This can be seen by the analysis of statistical data which shows a significant result with p value of 0.015.

The weakness of this study is the assumption that the two groups have homogeneous background especially in nutrition intake. Food recall was not conducted prior to this study.

## Conclusion:

Omega 3 and vitamin E combination supplementation can reduce the preeclampsia incidence.

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