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# Calcium supplementation dose and vegetable intake determine preeclampsia

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**ABSTRACT**

Preeclampsia is one of the causes of high maternal mortality rates. Risk factors for preeclampsia include a lack of nutrients such as vitamin A, calcium, sodium and potassium. Calcium intake in pregnant women is not only obtained from calcium supplementation, but also obtained from consumed foods such as vegetables. to analyzed the relationship between calcium supplementation dose and vegetable intake with preeclampsia in third trimester of pregnant women. Observational analytic used a prospective Cohort design. A total of 65 third trimester pregnant women participated in the study in Bantul, Yogyakarta. The calcium supplementation dose was obtained through interview using a questionnaire, while vegetable intake was obtained through the food frequency and food recall 2x24 hours. 16 third trimester pregnant women experienced preeclampsia. The mean calcium dose consumed per day was 476.2 mg. The average intake of vegetables per day for pregnant women was 250.9 gr. Kaplan-Mier with the log rank method states that there was a significant difference between calcium supplementation dose (p=0.007) and preeclampsia. There was a significant difference between vegetable intake (p=0.007) and preeclampsia. There was a significant relationship between calcium supplementation dose and vegetable intake with preeclampsia in third trimester pregnant women.



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## 1. INTRODUCTION

Preeclampsia is a progressive multisystem disorder characterized by the appearance of hypertension and proteinuria, or hypertension and organ dysfunction without proteinuria that occurs at more than 20 weeks of gestation. Preeclampsia can cause organ dysfunction and disease in both the mother and fetus. Severe preeclampsia in pregnant women can cause an increased risk of diastolic dysfunction and peripartum pulmonary edema and can subsequently cause an increased risk of cardiovascular disease [1]. In the fetus with preeclampsia mother, it can cause fetal development disorders and associated with an increased risk of bronchopulmonary dysplasia in infants [2].

Based on the health profile of Bantul Regency, Yogyakarta, the Maternal Mortality Rate (MMR) in 2017 was 72.85/100,000 live births, nine cases and two of them caused by preeclampsia [3]. The cause of preeclampsia is not clearly known and influenced by several factors. Some studies show that preeclampsia is caused by an increase in oxidative stress. There is a significant relationship between nutrient intake and antioxidant status in mothers suffering from preeclampsia [4].

In preeclampsia, due to failure of trophoblastic invasion, an inadequate blood perfusion accurs leading to areas of ischemia and reperfusion which increases the generation of ROS and cause activation of neutrophils and leukocytes. ERO is the most common Superoxide ($O_2^-$), generated by NADPH oxidase in cells, xanthine oxidase enzymes and the electron transport chain of mitochondria. Neutrophils isolated from women with preeclampsia synthesize more superoxide than normal pregnant women, and this is mediated by NADPH oxidase [5]. Intake of certain nutrients is known to be associated with preeclampsia such as vitamin A, calcium, sodium, and potassium. Micronutrients such as vitamin A can trigger oxidative stress and subsequently contribute to inflammation through cell-mediated Nuclear Factor-Kappa B (NF-κB-) pathway and produce free radicals [6]. Sources of vitamins and minerals can be obtained from vegetables intake in daily food consumption.

WHO recommends taking 1.5-2 gr/day calcium supplements to meet daily requirement of calcium intake needed from food. Calcium supplementation can work well if used regularly by the pregnant women. Previous research has not examined much about the relationship between the ideal dose of calcium supplementation in order to prevent the occurrence of preeclampsia. Therefore, this study aims to analyse the relationship between calcium supplementation dose and vegetable intake with the incidence of preeclampsia in third trimester pregnant women.

## 2. RESEARCH METHODS

This research was an observational analytic, using a prospective Cohort design. The study was carried out during July-September 2018 in the Bantul district health center in Yogyakarta. The sample was collected using simple random sampling technique by randomize third trimester pregnant women to take five pregnant women in each puskesmas. Inclusion criteria in this study included: age 20-35 years, routine antenatal care (ANC) in the third trimester. Exclusion criteria: having a history of diabetes mellitus, hypertension, preeclampsia, and obesity.

Sociodemographic data were obtained using questionnaires which filled by respondents. Sociodemographic data obtained from respondents were age, parity, employment, and education status of pregnant women. Data on calcium supplementation included adherence of pregnant women to take calcium supplements. Data was obtained through interviews and through filling a questionnaire containing questions that have been tested for validity and reliability. The results of the validity test stated that all question items in the questionnaire on each variable were valid ($r_{count}>0.33$) and reliable ($r_{CronbachAlpha}>0.6$). Vegetable intake was obtained through interviews with enumerators by using a 2x24 hour food frequency and food recall questionnaire. Vegetable intake was then categorized into 2, which was sufficient (≥250 gr/day) and less (<250 gr/day). Examination and assessment of the signs of preeclampsia were carried out by experts who include blood pressure, facial and extremities edema, and urine protein from the KIA (maternal and children health) books classified according to the midwifery book [7].

Categorical variables were showed as frequency and percentage, while continuous variables are showed as mean±SD. Bivariate analysis with the Kaplan-Mier test was conducted to examine the relationship between each independent variable with the incidence of preeclampsia. Multivariate analysis by using Cox regression test was used to determine the most influential variables and find the value of hazard ratio. Proportional hazard assumption test was carried out before the multivariate test. The significant statistic value was $p<0.05$. Ethical approval and clearance was obtained from the health research ethics committee of faculty of medicine, Sebelas Maret University. Informed consent was obtained from each individuals and confidentiality was kept.

## 3. RESULTS AND DISCUSSION

### 3.1. Characteristics of pregnant women

The characteristics of pregnant women are shown in Table 1. The study subjects are third trimester pregnant women with range of age 20-35 years. The average age of third trimester pregnant women is 26.3±3.95 years. Most pregnant women with multigravida parity (>1 times) is 50.8%. Parity of a woman can affect the psychological health, especially in the third trimester pregnant women who will undergo delivery process. The results showed that most pregnant women worked as entrepreneurs (52.3 %) and most of them were high school graduates (61.5%). Higher mother's education, associated with better knowledge and more mature intellectual.

### 3.2. Association between calcium supplementation dosage and vegetable intake with preeclampsia

The mean dose of consumed calcium by the third trimester of pregnancy is 476.2 mg/day. The average dose of calcium consumed by pregnant women who have preeclamsia is 435.5 mg/day,

whereas in pregnant women who do not preeclamsia is 489.5 mg/day. The common type of calcium supplement is given by puskesmas to pregnant women are calcium lactate (78.5%), while the rest is in the form of calsifar (12.3%) and licokalk (7.7%).

Table 2 reveals results of Kaplan-Mier's statistical test using the log rank method. It shows a significant difference between the average dose of calcium supplements per day consumed by third trimester pregnant women with preeclampsia compared to third trimester pregnant women without preeclampsia ($p<0.001$). Supplementation of calcium with vitamin D for 9 weeks, may decrease plasma fasting glucose and lipid profile in pregnant women and will reduce the risk of preeclamsia ($p<0.05$) [8].

Table 1. Characteristics of pregnant women

| Variable | Preeclampsia incident | | Total(%) | p Value |
|---|---|---|---|---|
| | No | Yes | | |
| Age ($\bar{x}$ ±SD, year) | 25.96±3.94 | 28.75±3.19 | | 0.087 |
| Parity, n (%) | | | | 0.028* |
| Primigravida | 28(43.1) | 4(6.2) | 32(49.2) | |
| Multigravida | 21(32.3) | 12(18.5) | 33(50.8) | |
| Occupation, n (%) | | | | 0.511 |
| Labour | 6(9.2) | 1(1.5) | 7(10.8) | |
| Farmers/ traders | 5(7.7) | 4(6.2) | 9(13.8) | |
| Teacher | 4(6.2) | 0(0.0) | 4(6.2) | |
| Housewive | 8(12.3) | 3(4.6) | 11(16.9) | |
| Enterpreneur | 26(40.0) | 8(12.3) | 34(52.3) | |
| Income, n (%) | | | | 0.266 |
| <1,000,000 | 3(4.6) | 0(0.0) | 3(4.6) | |
| 1,000,000–2,000,000 | 38(58.5) | 11(16.9) | 49(75.4) | |
| >2,000,000 | 8(12.3) | 5(7.7) | 13(20.0) | |
| Education, n (%) | | | | 0.970 |
| Elementary school | 5(7.7) | 0(0.0) | 5(7.7) | |
| Junior High school | 6(9.2) | 2(3.1) | 8(12.3) | |
| Senior High School | 32(49.2) | 8(12.3) | 40(61.5) | |
| College | 3(4.6) | 0(0.0) | 3(4.6) | |
| University | 8(12.3) | 1(1.5) | 9(13.8) | |

$\bar{x}$±SD=average±standard deviation
n=number,%=percentage
*p<0.05 using the Kaplan-Mier test with the log rank method

Table 2. Association between calcium supplementation dose and vegetable intake with the incidence of preeclampsia

| Variable | Preeclamsia Incidence | | Total(%) | p value |
|---|---|---|---|---|
| | No | Yes | | |
| Calcium Dose | | | | 0.007* |
| Less | 17(26.2) | 12(18.5) | 31(44.6) | |
| Enough | 32(49.2) | 4(6.2) | 34(55.4) | |
| Vegetable Intake | | | | 0.007* |
| Less | 25(38.5) | 14(21.5) | 39(60.0) | |
| Enough | 24(36.9) | 2(3.1) | 26(40.0) | |

$\bar{x}$±SD = average±standard deviation
*$p$<0.05 using the Kaplan-Mier test with the Log Rank methods

To obtain a plot graph of the pregnant woman resilience to remains normal experiencing preeclampsia in the third trimester, both trimester III pregnant women take calcium supplements with adequate or less doses, the researchers used the survival function chart is shown in Figure 1. The graph shows that the third trimester pregnant women who take enough doses calcium supplements (≥500 mg/day) had a survival rate higher than third trimester pregnant women who take calcium supplements at a less dose (<500 mg/day) as shown in Figure 1.

Low calcium intake causes an increase in parathyroid hormone (PTH) and renin, so it will causes an increase in intracellular calcium, vasoconstriction and hypertension. Extracellular calcium density will increase according to increased calcium intake and will reduce the secretion of Nitric Oxide (NO) produced by vascular endothelium. The role of calcium supplementation in reducing the symptom of preeclampsia such as hypertension is by the release of intracellular calcium concentration, reducing the smooth muscle contractility and promotes vasodilation [9].

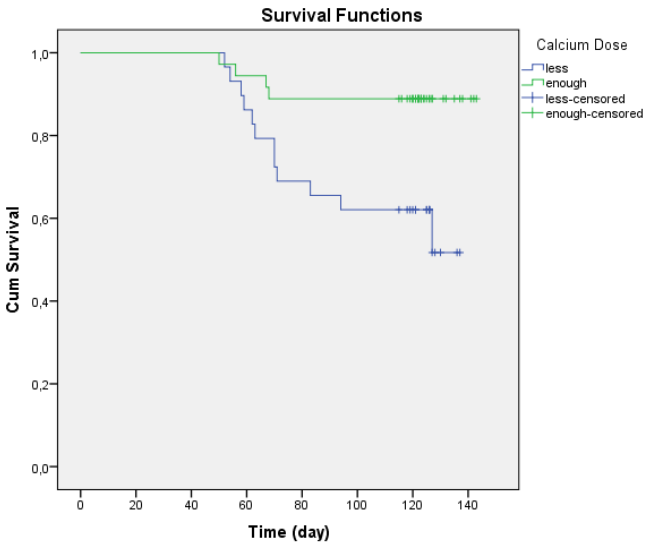


Figure 1. Survival function graph of calcium supplementation dose in third trimester pregnant women

Figure 2 shows vegetable intake survival function graph in third trimester pregnant women. The reason pregnant women did not take calcium supplements in this study was that most of them said they felt nauseous after taking calcium supplements (54.3%), respondents also said they often forgot to take it (28.6%), it smelled bad (8.6%) , and said that they felt healthy and did not need to take supplements (5.7%). Pregnant women to consume micronutrient supplements such as iron and calcium for 90 days is influenced by several factors namely distance of house, urbanization, ANC visit, maternal age, knowledge and financial condition [10]. Other studies state that the condition such as nausea, vomiting, and forgetting to take supplements because of busy reasons is an obstacle for pregnant women to comply with recommended recommendations for supplements consumption [11].

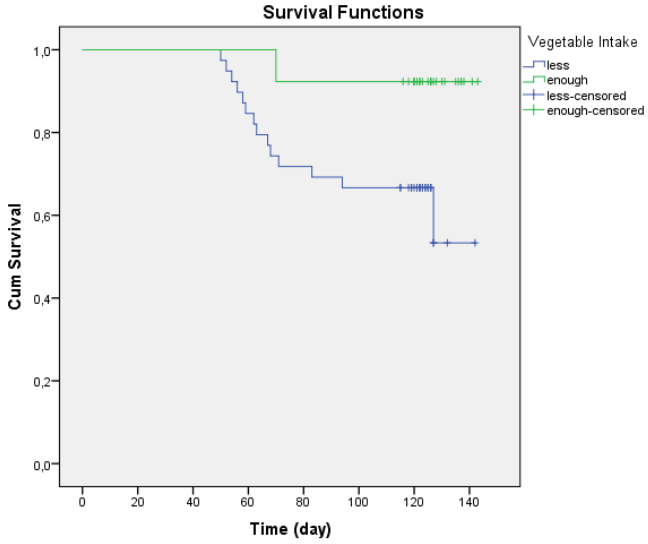


Figure 2. Vegetable intake survival function graph in third trimester pregnant women

Table 2 shows that there is a significant difference between vegetable intake (p=0.007) and the incidence of preeclampsia. Vitamin A in the form of retinol, retinal and retinoid acid is believed to be an antioxidant that is effective in inhibiting free radicals formation. Vitamin A can be obtained from various food sources such as green and yellow vegetables, milk, fruits and red meat. Antioxidants like vitamin A and

ß-carotene which are very rich all seasonal vegetables with vivid colors stand as prophylactic [12]. Low levels of antioxidants, or inhibition of the antioxidant enzymes, cause oxidative stress and may damage or kill cells. Antioxidant activity in vitamin A is produced in the form of compounds from hydrophobic chains in polyene units that can eliminate singlet oxygen, neutralize ethyl radicals and make peroxyl radical stable [13].

Antioxidants in vitamin A protect polyunsaturated fatty acids and lipoproteins that are between membranes from the peroxidation process. Pregnant women with preeclampsia have increased levels of peroxidation products found in saliva, urine and plasma. Plasma concentration of the isoprostane 8-iso-prostaglandin F2α (8-iso-PGF 2) which is a peroxidation product increases in pregnant women with preeclampsia compared to normal pregnant women [14]. Therefore, high vitamin a content in vegetable such as cassava leaf can inhibit lipid peroxidation processes and can reduce the risk of the occurrence of preeclampsia in pregnant women in the third trimester.

To obtain plot graph of pregnant women endurance to remain normal or develop preeclampsia in the third trimester, both third trimester pregnant women with adequate vegetable intake and third trimester pregnant women with less vegetable intake were analyzed. Researchers used a survival function graph (Figure 2). From the graph, it can be seen that third trimester pregnant women with adequate vegetable intake (≥250 gr/day) have a higher survival rate compared to third trimester pregnant women with less vegetable intake (<250 gr/day) as shown in Figure 2.

Table 3 shows the most influential variable to preeclampsia is vegetables intake by third trimester pregnant women (p=0.026). Five Types of vegetables that are often consumed by pregnant women are cassava leaf vegetables (85.3%), long beans (10.7%), and spinach (5%). Cassava leaves contain a lot of vitamin A which is in 100 grams of cassava leaves, there are 1,100 IU of Vitamin A. Vitamin A is a powerful natural antioxidant, besides it also contains very good vitamin A, and other antioxidants such as alpha and beta-carotene, beta-cryptoxanthin, zea-xanthin and lutein. This compound is known to have antioxidant properties. In food science, the oxygen radical absorbance capacity (ORAC) has become the current industry standard for assessing the antioxidant strength of whole foods, juices, and food additives [15]. The total antioxidant strength or Oxygen Radical Absorbance Capasity (ORAC) of cassava leaves was 1.510 µmol TE/100 gr and the peanut ORAC was 453 µmol TE/100 gr [16]. Oxidative stress and decreased antioxidant defense increase lipid peroxidation and cause radicals and will cause vascular endothelial damage. In preeclampsia patients there is a significant decrease in antioxidant activity (AOA), so vegetables containing high antioxidants such as cassava leaves can increase antioxidant defenses in the body [17].

Table 3. Cox regression test

| Variable | B | SE | Exp(B) | *p* value |
|---|---|---|---|---|
| Parity | 1.06 | 0.58 | 2.88 | 0.068 |
| Vegetable intake | -1.69 | 0.76 | 0.18 | 0.026* |

*$p<0.05$, using the Cox Regression test

Cassava leaves contain minerals such as iron (2 mg/100 gr) and calcium (16 mg/100 gr). Fetus requires calcium for bone formation. To meet calcium needs, fetus takes calcium from its mother. Approximately 200 mg/day calcium is stored in the skeleton in the third trimester, reaching 25 to 30 gr [18]. In addition, excretion of calcium through urine at the end of pregnancy, on average, doubled compared with non-pregnant women. This causes decrease calcium levels in pregnant women. In other study, low dietary calcium intake may be a risk factor or risk marker for the development of hypertension, which can lead to preeclampsia [19]. Vegetable intake that contains a lot of potassium such as long beans will increase potassium in intracellular fluid, tends to attract fluid from the extracellular part and can reduce blood pressure to prevent the occurrence of preeclampsia [20].

## 4. CONCLUSION

Based on the results, there is a significant relationship between calcium supplementation dose and vegetable intake with preeclampsia incidence in third trimester pregnant women ($p<0.05$). Health workers are expected to actively provide guidance on how to take calcium supplements correctly and amount consumed each day. The results of this study are expected to provide knowledge to pregnant women to always pay attention on how many calcium supplement tablets should be consumed per day and adequate vegetable intake in order to avoid preeclampsia.

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