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ORIGINAL ARTICLE

DOSE AND DURATION OF CALCIUM SUPPLEMENTATION ON PRE-ECLAMPSIA: A CASE CONTROL STUDY

Dosis dan Lama Suplementasi Kalsium Pada Pre-Eclampsia: Studi Kasus Kontrol

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ABSTRACT

Background: Pre-eclampsia is one of the causes of high maternal morbidity and mortality. The WHO has recommended calcium supplementation based on dose and duration in pregnant women to reduce the risk of pre-eclampsia. However, the calcium supplementation program in Indonesia is not following the WHO recommendations. **Objective:** This study aimed to analyze the dose and duration of calcium supplementation on the occurrence of pre-eclampsia. **Methods:** This research is an observational study with a case-control design. The study was conducted from June to August 2021. The study participants are pregnant women in the third trimester in Madiun District, consisting of 42 case groups and 98 control groups with random cluster sampling. Simple logistic regression was used to analyze the relationship between dose and duration of calcium supplementation variables on the variable of pre-eclampsia. **Results:** Calcium dose showed calcium consumption < 3 doses/day had odds of 2.54 times compared to calcium intake 3 doses/day [95%CI = 1.02-6.35]. The duration of calcium supplementation showed that calcium administration after 20 weeks had odds of 0.45 times [95%CI = 0.21-0.98] compared to calcium administration before 20 weeks of gestation on the occurrence of pre-eclampsia. **Conclusion:** Calcium supplementation based on dose and duration was associated with the occurrence of pre-eclampsia. It was recommended for pregnant women to consume calcium supplements with the right dose and duration to reduce the risk of pre-eclampsia.

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ABSTRAK

Latar Belakang: *Pre-eklampsia merupakan salah satu penyebab tingginya morbiditas dan mortalitas ibu. WHO telah merekomendasikan suplementasi kalsium berdasarkan dosis dan durasi pada ibu hamil sebagai upaya penurunan risiko pre-eklampsia. Namun demikian program suplementasi kalsium di Indonesia belum sesuai dengan rekomendasi WHO.* ***Tujuan:*** *Penelitian ini bertujuan menganalisis dosis dan durasi suplementasi kalsium terhadap terjadinya pre-eklampsia.* ***Metode:*** *Penelitian ini merupakan penelitian observasional dengan desain case-control. Penelitian dilakukan pada bulan Juni hingga Agustus tahun 2021. Populasi penelitian merupakan ibu hamil trimester tiga di Kabupaten Madiun, sampel sejumlah 42 kelompok kasus dan 98 kelompok kontrol dengan cluster random sampling. Analisis chi-square digunakan untuk menganalisis hubungan variabel dosis dan durasi suplementasi kalsium terhadap variabel pre-eklampsia.* ***Hasil:*** *Dosis kalsium menunjukkan konsumsi kalsium < 3 dosis/hari memiliki odd* 2.54 *kali dibandingkan dengan konsumsi kalsium 3 dosis/hari* [95%CI = 1.02 – 6.35]. D*urasi suplementasi kalsium menunjukkan pemberian kalsium pada usia kehamilan setelah 20 minggu memiliki odd 0.45 kali* [*95%CI =* 0.21 – 0.98] *dibandingkan dengan pemberian kalsium sebelum usia kehamilan 20 minggu terhadap terjadinya pre-eklampsia.* ***Kesimpulan:*** *Suplementasi kalsium berdasarkan dosis dan durasi berhubungan dengan terjadinya pre-eklampsia. Disarankan kepada ibu hamil untuk mengkonsumsi suplemen kalsium sesuai dengan dosis dan durasi yang tepat sebagai upaya mengurangi risiko terjadinya pre-eklampsia.*

INTRODUCTION

Pre-eclampsia is the second leading cause of maternal death causing 500,000 fetal and neonatal deaths and an estimated 76,000 maternal deaths every year (1). In Indonesia hypertension in pregnancy was the second highest cause of maternal mortality in 2020 as many as 1,110 cases, after bleeding as many as 1,330 cases (2). Whereas in East Java in 2019 pre-eclampsia/eclampsia was ranked first as the cause of maternal death (3). Pre-eclampsia is described as hypertension that develops after 20 weeks of pregnancy with one or more of the following symptoms: proteinuria, maternal organ dysfunction (including renal, hepatic, hematological, or neurological problems), or fetal growth restriction are all possible causes of fetal growth restriction (4).

The third goal of SDGs 2030, namely a healthy and prosperous life, has the indicator of reducing maternal mortality. In Indonesia, in general, there was a decrease in maternal mortality during the period 1991-2015 from 390 to 305 per 100,000 live births. Although there is a tendency to decrease maternal mortality, it has not succeeded in achieving the MDGs target of 102 per 100,000 live births in 2015 (5). In 2019, the MMR in East Java Province reached 89.81 per 100,000 live births. Madiun District ranks third with the highest maternal mortality rate in East Java, namely 146.64 per 100,000 live births. The highest causes of maternal death in East Java in 2019 were pre-eclampsia/ eclampsia at 31.15%, bleeding 24.23%, other causes 23.08%, metabolic disorders 13.85%, infection 6.73%, and circulatory disorders by 0.38% (3).

Pre-eclampsia is a multifactorial disorder. Risk factors that can affect pre-eclampsia are age, gravida status, history of heredity, antenatal examination, history of pre-eclampsia, history of hypertension, primigravida, obesity, calcium supplements (6,7). Calcium supplements play a role in the prevention of pre-eclampsia (8). The World Health Organization (WHO) recommends calcium supplementation for pregnant women at 1,500-2,000 mg/day, with the total dose divided into three doses, the duration of administration at the first antenatal care contact as an effort to reduce the risk of pre-eclampsia (9).

The importance of integrating calcium supplements at antenatal visits (10). However, this recommendation has not become a mandatory program for the Indonesian Ministry of Health, calcium supplementation is given according to indications. In Indonesia, calcium supplementation of 1,500–2,000 mg/day is indicated for the

prevention of pre-eclampsia in pregnant women starting at 20 weeks of pregnancy (11).

Several studies have described the relationship between calcium supplementation with maternal blood pressure and the incidence of pre-eclampsia. Calcium supplementation is associated with lowering blood pressure, especially for pregnant women who are at high risk and with low calcium supplementation (12). This study aims to analyze the dose and duration of calcium supplement on pre-eclampsia cases in pregnant or postpartum women to prevent pre-eclampsia which has an impact on reducing maternal morbidity and mortality.

METHODS

This study was observational because we did not give treatment to the subjects studied. The type of analytical research was research to examine the relationship between exposure and its consequences, which aims to obtain an explanation of the causative factors by comparing the risk of disease between the exposed and non-exposed groups. This study was a case-control study design that this study examines the relationship between exposure and disease by comparing the case group and control group based on their exposure status. This study looked at the incidence of pre-eclampsia and then analyzed age, education, income, and calcium supplementation (dose and duration of calcium supplements).

The hypothesis test formula for the calculation of the Odds Ratio (OR) published by Lemeshow was used to determine the number of samples required for the investigation. The type I error tolerance was 5%, and the research power was 80%, according to the case-control design. The sample size was 140 participants, based on the literature study and case restrictions. This study used 1: 2 case-control ratio, 42 patients and 98 controls were used in the study.

Based on data on pre-eclampsia cases from the Madiun District Health Office for the period January to April 2021, seven health centers from 26 public health centers in the Madiun Regency area were determined by considering the sites with the most pre-eclampsia cases as research sites. The sample size was determined proportionally with a ratio of 1: 2 at seven public health centers to obtain a total of 42 cases and 98 controls. This research was conducted from June to August 2021 at the Public Health Center in Madiun District, East Java.

The case population used was women who had pre-eclampsia, namely pregnant women who had blood pressure 140/90 mmHg and accompanied by proteinuria (above positive 1) and or without edema at the time of gestation between 20 weeks and before delivery based on the doctor's diagnosis judging by the mother's register. The control population was pregnant women who were not pre-eclampsia based on the maternal register.

The inclusion criteria in this study were mothers who had a maternal and child health book and pregnant women who were in the Madiun District Health Center area. The exclusion criteria were mothers with experience of anemia, diabetes mellitus, chronic kidney disease, history of hydatidiform mole, pre-eclampsia offspring, and multiple pregnancies, which were carried out by filling out a screening questionnaire and validated with the maternal and child health book. A sampling of the case population took into account the limitations of cases so that all cases during the data collection period were taken with a minimum sample of 42 cases. Meanwhile, sampling in the control population was carried out by simple random sampling to obtain a sample of 98.

The independent variables in this study were sociodemographic characteristics including age categorized into high-risk age with code 1 (less than 20 years and more than 35 years) and low-risk age with code 2 (20-35 years). Education was categorized into low with code 1 (for those who are not in school, elementary school, and junior high school), medium with code 2 (upper secondary school), and high with code 3 (higher education diploma, bachelor, doctorate). Income was divided into low with code 1 (below the district minimum wage, which is less than 2 million rupiah) and high income with code 2 (above the district minimum wage, which is 2 million rupiah or more). Calcium supplementation was based on the dose of calcium administration which is categorized into giving calcium less than 3 doses/day (1,500 mg/day) with code 1 and giving calcium 3 doses/day with code 2.

Based on the duration of calcium administration was categorized as being given since 20 weeks of gestation with code 1 and less than 20 weeks with code 2 (9,11). The dependent variable was pre-eclampsia status with code 1 and non pre-eclampsia with code 2. The questionnaire has been tested for validity and reliability. Date collection used secondary data from medical records and books on Maternal and Child Health and primary data in the form of filling out

questionnaires. A computer application program was used to process the information. Data were analyzed using simple logistic regression. This study was approved by Universitas Airlangga, Faculty of Dental Medicine Health Research Ethical Clearance Commission with a letter-number 196/HRECC.FODM/IV/2021 and respondent's consent by signing the informed consent.

RESULTS

Table 1 reveals that 75.71% of mothers are between the ages of 20 and 35, that more than half (53.57%) have a secondary education, and that 75.00% have a low family income (below the Regional Minimum Wage). With a length of 70.00% calcium supplied from less than 20 weeks gestation, doses of calcium supplements were virtually exclusively 83.57% fewer than three doses per day.

Table 1
Frequency Distribution of Sociodemographic Characteristics, Calcium Supplementation, Pre-eclampsia in Madiun District 2021

Variable	n	%
Characteristics		
Age		
High risk	34	24.29
Low risk	106	75.71
Education		
Low	39	27.86
Medium	75	53.57
High	26	18.57
Income		
Low	105	75.00
High	35	25.00
Calcium supplementation		
Calcium dose (doses/day)		
< 3	117	83.57
3	23	16.43
Calcium duration (weeks)		
≥ 20	40	28.57
< 20	100	71.43
Pre-eclampsia		
Pre-eclampsia	42	30.00
No Pre-eclampsia	98	70.00
Total	140	100.00

Table 2 presents that if a mother is under 20 years old and over 35 years old, she has a 0.37 likelihood of developing pre-eclampsia compared to those with a low risk (20-35 years) [OR= 0.37; 95% CI = 0.16-0.82]. When compared to high income (above the district minimum pay), poor income (below the district minimum wage) has 2.56 times the odds of having pre-eclampsia [OR = 2.56; 95% CI = 1.15-5.69]. When calcium supplementation was less than three doses per day, the risk of pre-eclampsia was 2.54 times higher [OR = 2.54; 95% CI = 1.02-6.35] than when it was three doses per day. When calcium supplementation was provided at a gestational age greater than or equal to 20 weeks, the risk of reducing pre-eclampsia was 0.45 times than when calcium supplementation was given at a gestational age less than 20 weeks [OR = 0.45; 95% CI = 0.21-0.98]. The results are shown in our study that pre-eclampsia was higher at the age of 20-35 years by 61.91%.

DISCUSSION

Pre-eclampsia is one of the causes of maternal and infant mortality; risk factor analysis plays a role in preventing the occurrence of pre-eclampsia. The results of the study showed that the sociodemographic characteristics of the mother that were shown to be significant in the risk of pre-eclampsia were age and income. Dose and duration of the calcium supplementation are also significant. Proof that age is associated with the occurrence of pre-eclampsia was found in a study conducted in Northern Tanzania, South India, which found that mothers with extreme ages of less than 20 years and over 35 years are at higher risk of developing pre-eclampsia (13,14).

Family income is associated with the ability of the mother's family to reach good and adequate health facilities and fulfill nutrition during pregnancy (15). Family income is identified based on the results of the family's income in meeting their daily needs every month based on the Decree of the Governor of East Java No. 188/538/KPTS/013/2020 concerning the Madiun District Minimum Wage in 2021. This result is in line with a study conducted in Sukoharjo which found that there is a relationship between mothers with high economic status and having a 2.34 times greater chance of not having pre-eclampsia compared to mothers with low family economic status (16). Low socioeconomic status influences health behavior, which is characterized by high cases of pre-eclampsia (17).

Table 2
Relationship between Sociodemographic Characteristics, Calcium Supplementation, and Cases of Pre-eclampsia in Madiun District 2021

Variable	Pre-eclampsia status				p-value	OR 95%CI
	Pre-eclampsia		Non Pre-eclampsia			
	n	%	n	%		
Sociodemographic Characteristics						
Age					0.01*	
High risk	16	38.09	18	18.37		0.37 (0.16 – 0.82)
Low risk	26	61.91	80	81.63		Ref
Education					0.39	
Low	13	30.95	26	26.53		1.25 (0.45 – 3.51)
Medium	19	45.24	56	57.14		1.84 (0.72 – 4.74)
High	10	23.81	16	16.33		Ref
Income					0.02*	
Low	26	61.91	79	80.61		2.56 (1.15 – 5.69)
High	16	38.09	19	19.39		Ref
Calcium supplementation						
Calcium dose (doses/day)					0.04*	
< 3	31	73.81	86	87.76		2.54 (1.02 – 6.35)
3	11	26.19	12	12.24		Ref
Calcium duration (weeks)					0.04*	
≥ 20	17	40.48	23	23.47		0.45 (0.21 – 0.98)
< 20	25	59.52	75	76.53		Ref
Total	42	100.00	98	100.00		

Dose of the calcium supplementation was significantly related to the occurrence of pre-eclampsia. Our findings revealed that a calcium supplementation dose of less than three doses per day (1,500 mg/day) was linked to an elevated risk of pre-eclampsia when compared to three doses per day. This is in line with a research which explained that insufficient supplementation of calcium supplements during pregnancy increases the risk of pre-eclampsia by 3.8 times compared to adequate supplementation of calcium (18).

The pathophysiology of pre-eclampsia is that anomalies in the placenta can produce substances that are secreted in the maternal blood circulation, resulting in pre-eclampsia clinical symptoms that arise after 20 weeks of pregnancy (19). The role of calcium supplementation on the risk of pre-eclampsia and eclampsia is by reducing parathyroid calcium release and intracellular calcium concentration, resulting in decreased smooth muscle contraction and vasodilation (20).

Low calcium intake causes an increase in parathyroid hormone and renin, thereby causing an increase in intracellular calcium, vasoconstriction, and hypertension. Extracellular calcium density will increase according to the increase in calcium intake. The role of calcium supplementation in reducing pre-eclampsia symptoms such as hypertension is by releasing intracellular calcium concentrations, reducing smooth muscle contractility and increasing vasodilation (21).

Study explains that there is a relationship between the dose of calcium supplementation and the occurrence of pre-eclampsia (22–25). A systematic review also found that daily dosages of 1200–2000 mg are linked to a lower incidence of pre-eclampsia (26).The dose of calcium consumed by pregnant women who have pre-eclampsia shows a low dose (less than 500 mg/day), while pregnant women who are not pre-eclampsia consume calcium supplements with high doses (27). Nevertheless, there are results of a systematic review that explain that calcium supplements have a certain effect in preventing the occurrence of pre-eclampsia, but there is no comparison of the effects of different doses of calcium supplements, namely the three doses of calcium supplements can reduce the risk of pre-eclampsia (26).This is because differences in populations in developed countries do not show significant differences in calcium doses because they are met from food intake.

A randomized controlled trial (RCT) study proved the effect of calcium supplementation

given before pregnancy or less than 20 weeks of gestation is effective in reducing the risk of pre-eclampsia (28). Pregnant women who consume calcium supplements for more than six months during pregnancy have a 45% lower risk of developing hypertension compared to pregnant women who consume calcium supplements for less than three months (29).

Our results show that calcium administration more than equal to 20 weeks is significant in protecting against pre-eclampsia. In line with the research by Khaing et al (21), calcium supplementation has been demonstrated to be more beneficial at 20 weeks of pregnancy or more, in addition to the dose.

This study contrasts with the WHO recommendation of giving calcium supplements at the first antenatal visit, aiming to improve maternal compliance (9). This is because the obstacle for pregnant women to comply with recommendations in consuming supplements is the factor of forgetting to take supplements (30). Calcium supplements given at the first visit of pregnant women during antenatal care have been shown to be effective in increasing the compliance of pregnant women in consuming calcium, which has an optimal effect in preventing pre-eclampsia (10). The WHO explains that there is not enough evidence to determine the exact gestational age how much calcium supplementation should be started to provide a benefit in reducing the risk of pre-eclampsia (9). Compliance with calcium supplement consumption is related to the effects of nausea caused (30) which will be exacerbated if calcium supplements are given in early pregnancy.

Previous studies have related to calcium supplementation in general and used 2013 WHO recommendations. This study provides specific information regarding the dose and duration that affect the occurrence of pre-eclampsia by 2018 WHO recommendations. The results of the study did not use an adjusted odds ratio, with the reason that the results did not show a significance after adjustment for age and education.

CONCLUSION

The occurrence of pre-eclampsia is linked to calcium supplementation based on dose and duration. More study on the minimal effective dose of calcium supplementation and the route of administration of prenatal supplements is required.

CONFLICT OF INTEREST

There are no competing interests declared by the authors.

AUTHOR CONTRIBUTIONS

EQ, RA, NMGN: Conceptualization, Methodology, Software. EQ, RA, SAS: Data curation, Writing- Original draft preparation. EQ, RA: Visualization, Investigation. EQ, RA: Supervision. SAS: Software, Validation. EQ, RA, SAS, NMGN: Writing- Reviewing and Editing.

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