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# Ratio of Serum Calcium to Magnesium Levels on Pregnancy with and without Preeclampsia

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**Background:** Preeclampsia increases maternal and perinatal mortality and is affected by calcium and magnesium levels. Reduced extracellular levels of calcium and magnesium constitute the pathogenesis of eclampsia. A reduction in the calcium-magnesium ratio may aid in the detection and prevention of preeclampsia.

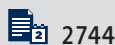
**Material/Methods:** This was an analytical observational study with a cross-sectional design, including patients with and without preeclampsia (inpatient and outpatient). A total of 246 patients were included in this research; 138 patients had preeclampsia and 108 patients did not. All examinations of magnesium and calcium levels at the Hasan Sadikin Hospital Clinical Pathology laboratory were conducted using an ion selective electrode modified with methylthymol blue complexometric titration.

**Results:** Patients with preeclampsia had significantly higher average serum magnesium and calcium levels than did patients without preeclampsia (2.85 vs 2.09,  $P=0.0001$ ; 4.45 vs 4.85,  $P=0.025$ , respectively). Patients with preeclampsia demonstrated significantly lower serum calcium-magnesium ratios than did patients without preeclampsia (1.98 vs 2.60,  $P=0.0001$ ). Receiver operating characteristic curve analysis on the serum calcium-magnesium ratio showed an area under the curve of 68.0% ( $P=0.0001$ ), with a cutoff value of 2.36 (sensitivity 64.8%, specificity 62.3%), indicating that patients with serum calcium-magnesium ratios of  $<2.36$  were predicted to have a risk of preeclampsia.

**Conclusions:** Patients with preeclampsia had significantly lower serum calcium-magnesium ratios than did patients without preeclampsia; therefore, a low calcium-magnesium ratio could be a risk factor for preeclampsia.

**Keywords:** Calcium • Magnesium • Preeclampsia Eclampsia 2 • Pregnancy Complications

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/932032>



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## Background

Hypertension in pregnancy is one of the 3 main causes of maternal mortality, accounting for 25% of total maternal deaths worldwide [1,2]. Preeclampsia is a syndrome marked by hypertension and involvement of other organs and/or fetal growth disorder [3]. Preeclampsia is a specific condition that occurs only in pregnancy and is characterized by placental dysfunction and maternal response to systemic inflammation, with endothelial activation and coagulation [4]. Preeclampsia cases are more common in developing countries than in developed countries [5].

Although there have been many studies on preeclampsia, its specific etiology and pathophysiology remain unknown [5]. However, contributory factors include environmental factors and nutritional factors, namely calcium, magnesium, protein, lipids, and zinc [6].

Calcium and magnesium are ions that help maintain the membrane permeability potential of nerve and muscle cells. Magnesium competes with calcium ions for a presynaptic site. High magnesium concentrations inhibit acetylcholine release [7], while high calcium concentrations increase acetylcholine release from presynaptic nerve terminals. During cell injury and cell death, there is an influx of calcium ions into cells, leading to an increase in intracellular calcium ions and a loss of calcium homeostasis. Since magnesium is physiologically antagonistic to calcium, an influx of magnesium during cell injury occurs in an attempt to reduce cellular injury by calcium. Therefore, low calcium and magnesium levels have been associated with the incidence of preeclampsia in previous studies [8].

Low extracellular calcium and magnesium concentrations can increase neuronal excitability, which disrupts physiological processes and causes long-term potentiation, pain transmission, epileptogenesis, and nerve damage, which can lead to eclampsia or convulsions in pregnancy. Moreover, calcium and magnesium supplementation have been widely recommended as modalities of preeclampsia prevention [8,9].

The use of combination values is frequently used to increase the function of 2 or more variables. For instance, the use of the ratio of calcium to magnesium has been used to assess sperm quality [10]. The neutrophil to lymphocyte ratio has been used as an indicator of postoperative survival in non-small-cell lung cancer, predictor of stroke, prognostic factor in colorectal cancer, and evaluation factor in Alzheimer disease [11-14]. The knowledge of the reduction in calcium-magnesium ratio may aid in the detection and prevention of preeclampsia. The aim of this study was to compare the serum calcium-magnesium ratio in pregnant women with and without preeclampsia.

## Material and Methods

This is an analytical observational study with a cross-sectional design involving patients with and without preeclampsia in inpatient and outpatient settings at the Department of Obstetrics and Gynecology of Dr. Hasan Sadikin Hospital, Bandung, Indonesia from May to September 2020.

Preeclampsia diagnosis was based on the obstetrics and gynecology diagnosis and management guidelines of Dr. Hasan Sadikin Hospital, where a diagnosis is made if there is hypertension caused by pregnancy accompanied by other organ system disorders at a gestational age above 20 weeks [15]. The inclusion criteria for preeclampsia patients were (1) pregnant women diagnosed with preeclampsia with a single live fetus with no congenital defects found by ultrasonography; and (2) patients with no degenerative diseases, no congenital heart defects, and no kidney disease. The diagnosis of preeclampsia was based on the guidelines of the American College of Obstetricians and Gynecologists (ACOG) (Table 1).

The inclusion criteria for patients without preeclampsia were (1) no history of pre-pregnancy hypertension or chronic hypertension and/or diabetes mellitus; (2) no preeclampsia diagnosed in the first, second, or third trimesters; (3) negative urine protein examination; (4) pregnancy with a single live fetus with no congenital defects found by ultrasonography; and (5) patient had no congenital heart defects or kidney disease. Patients in both groups were excluded for lysis or damage to the blood sample and incomplete administration data. Patients were recruited through consecutive sampling.

The determination of sample size with a confidence level of 99.8% and a power of 95% was calculated using the formula for categorical unpaired numeric data as follows:

$$n_1 = n_2 = 2 \left( \frac{(Z_\alpha + Z_\beta)S}{X_1 - X_2} \right)^2$$

$$n_1 = n_2 = 2 \left( \frac{((1.96 + 1.64)1.5)}{1} \right)^2$$

$$= 2 (50.12) = 100.24 \approx 101$$

The minimum sample size for each group was 101 patients, and thus the minimum total sample size was 202 patients.

Medical history taking, physical examination, and laboratory examination were conducted for all patients. Calcium and magnesium level examinations were done at the Clinical Pathology Laboratory, Clinical Pathology Section of the Faculty

**Table 1.** American College of Obstetricians and Gynecologists diagnostic criteria of preeclampsia [22].

Symptoms	Diagnostic criteria for preeclampsia
Blood pressure	Systolic blood pressure $\geq 140$ mmHg or diastolic blood pressure $\geq 90$ mmHg This blood pressure had occurred 2 times at least 4 h apart after 20 weeks of gestation in a woman with previously normal blood pressure.
	Systolic blood pressure $\geq 160$ mmHg or diastolic blood pressure $\geq 110$ mmHg
<b>And</b>	
Proteinuria	Proteinuria $\geq 300$ mg/24-h urine collection
	Protein-creatinine ratio $\geq 0.3$
	Dipstick reading +2
<b>Or in absence of proteinuria, there is 1 of the following symptoms</b>	
Other symptoms	Thrombocytopenia (platelet count less than 100 000 $\mu$ L)
	Impaired liver function (elevated blood concentrations of liver enzymes more than twice the upper limit of normal concentrations)
	Renal insufficiency: Serum creatinin more than 1.1 mg/dL
	Pulmonary edema
	Headache or unresponsiveness to medication
	Visual disturbances

of Medicine, Padjadjaran University, Dr. Hasan Sadikin Hospital using an ion selective electrode modified with methylthymol blue complexometric titration.

The study population was comprised of pregnant women who came to the Obstetrics and Gynecology Department of Dr. Hasan Sadikin Hospital, either through the outpatient clinic or emergency department. The patients who met the inclusion and exclusion criteria were informed of the study and sample-collecting procedures, and all willing patients provided their informed consent.

A sample of 3 mL of cubital venous blood was taken before any medical therapy and was tested for magnesium sulfate levels. The blood sample was put into the plasma separator tube and left for 30 min and was then centrifuged at 4000 rpm for 5 min. All samples were stored at  $-20^{\circ}\text{C}$ . The analysis of calcium levels used the ion selective electrode method with the electrolyte analyzer RAPIDlab 348EX from Siemens. Analysis of magnesium was conducted using the modified methylthymol blue complexometric titration method with MG Flex reagent no. DF57.

The data collected were processed and analyzed descriptively and analytically. The mean, standard deviation, median, and range of numeric data were calculated, while categorical

data were presented as a frequency and percentage. The normality test was carried out using the Kolmogorov-Smirnov test ( $n > 50$ ). The Mann-Whitney, chi-squared, Fisher's exact, Kolmogorov-Smirnov, and unpaired *t* test were performed to analyze the data, as appropriate.  $P < 0.05$  was considered statistically significant. Data analysis was done using SPSS version 24.0 for Windows.

## Results

In May to September 2020, 416 pregnant women came to Dr. Hasan Sadikin Hospital in Bandung; 174 had preeclampsia and 242 did not have preeclampsia. After analysis of the inclusion and exclusion criteria, 246 patients remained: 138 with preeclampsia and 108 without preeclampsia. The mean age of patients with preeclampsia was  $30.70 \pm 8.229$  years, with 55 (39.9%) primiparous, 75 (54.3%) multiparous, and 8 (5.8%) grandemultiparous patients, while the mean age for patients without preeclampsia was  $30.31 \pm 6.704$  years, with 25 (23.1%) primiparous, 76 (70.4%) multiparous, and 7 (6.5%) grandemultiparous patients. Patients with preeclampsia had significantly different parity ( $P = 0.020$ ), body mass index ( $P = 0.001$ ), and nutritional status ( $P = 0.024$ ) from patients without preeclampsia, but there was no difference in age ( $P = 0.416$ ) and gestational age ( $P = 0.445$ ) (Table 2).

**Table 2.** Comparison of patient characteristics in the 2 groups.

Variable	Preeclampsia n=138	No preeclampsia n=108	P value
<b>Age</b>			<b>0.416</b>
Mean±SD	30.70±8.229	30.31±6.704	
Median	31.50	31.00	
Range (min-max)	15.00-47.00	15.00-47.00	
<b>Parity</b>			<b>0.020</b>
Primiparous	55 (39.9%)	25 (23.1%)	
Multiparous	75 (54.3%)	76 (70.4%)	
Grandmultiparous	8 (5.8%)	7 (6.5%)	
<b>Gestational age</b>			<b>0.445</b>
Mean±SD	36.33±4.089	36.38±3.793	
Median	39.00	37.50	
Range (min-max)	25.00-40.00	24.00-40.00	
<b>Body mass index</b>			<b>0.001</b>
Mean±SD	30.60±5.208	28.14±5.266	
Median	29.60	27.05	
Range (min-max)	17.90-53.24	18.42-44.86	
<b>Nutritional status</b>			<b>0.024</b>
<18.5 (Underweight)	2 (1.4%)	1 (0.9%)	
18.5-24.9 (Normal weight)	21 (15.2%)	32 (29.6%)	
25.0-29.9 (Obesity)	49 (35.5%)	44 (40.7%)	
30.0-34.9 (Obesity class I)	36 (26.1%)	16 (14.8%)	
35.0-39.9 (Obesity class II)	18 (13.0%)	12 (11.1%)	
>40.0 (Obesity class III)	12 (8.7%)	3 (2.8%)	
<b>Blood pressure</b>			<b>0.0001</b>
Mean±SD	161.90±11.394	115.67±8.169	
Median	160.00	120.00	
Range (min-max)	130.00-200.00	100.00-130.00	

For numerical data, the *P* values were calculated using the unpaired *t* test if the data were normally distributed with the Mann-Whitney test if the data were not normally distributed. *P* value <0.05 is considered statistically significant.

Patients with preeclampsia had a higher average body mass index than did patients without preeclampsia (30.60 vs 28.14). In the nutritional status category in the preeclampsia group, 2 patients had an underweight nutritional status, 21 had a normal weight, while the remaining 115 had obesity. In the non-preeclampsia group, 1 patient had an underweight nutritional status, 32 patients had a normal weight, and 75 had obesity (Table 2).

The characteristics of the preeclampsia group are described in Table 3. Following the ACOG criteria regarding preeclampsia (Table 1), we assessed systolic and diastolic blood pressure, aspartate aminotransferase, alanine aminotransferase, ureum, creatinine, platelets, headache, blurred vision, and pulmonary edema in patients with preeclampsia. The presence of pulmonary edema in these patients was based on physical examination and chest radiology results (Table 3).

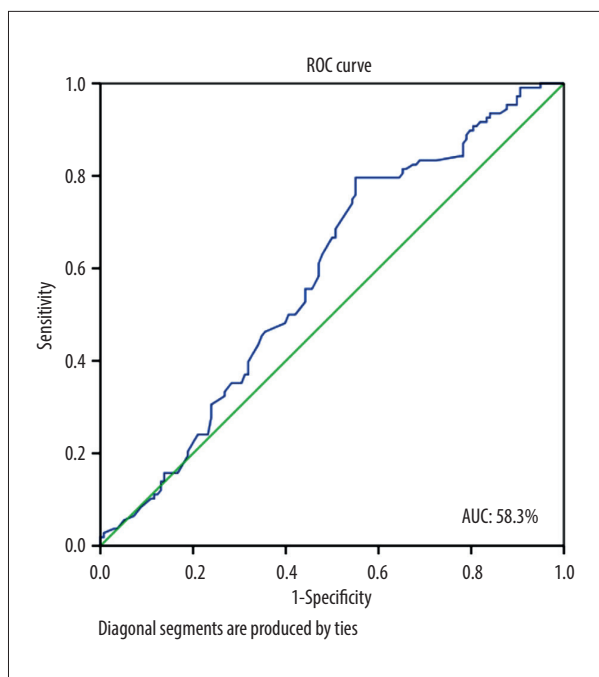
**Table 3.** Characteristics of preeclampsia in patients.

Variable	n=138	Variable	n=138
<b>Body mass index</b>		<b>Alanine aminotransferase</b>	
Mean±SD	30.60±6.208	Mean±SD	30.25±56.461
Median	29.60	Median	18.00
Range (min-max)	17.90-53.24	Range (min-max)	2.00-557.00
<b>Systolic blood pressure</b>		<b>Ureum</b>	
Mean±SD	161.90±11.394	Mean±SD	23.26±20.951
Median	160.00	Median	18.00
Range (min-max)	130.00-200.00	Range (min-max)	3.30-161.20
<b>Diastolic blood pressure</b>		<b>Creatinine</b>	
Mean±SD	100.57±5.613	Mean±SD	0.95±1.026
Median	100.00	Median	0.73
Range (min-max)	80.00-120.00	Range (min-max)	0.30-9.47
<b>Aspartate aminotransferase</b>		<b>Platelets</b>	
Mean±SD	45.86±114.990	Mean±SD	250.72±90.488
Median	24.00	Median	247.00
Range (min-max)	10.00-1108.00	Range (min-max)	1.00-456.00

**Table 4.** Comparison of serum calcium and magnesium levels and calcium-magnesium ratios in patients with and without preeclampsia.

Variable	Preeclampsia n=138	No preeclampsia n=108	P value
<b>Serum calcium level (mg/dL)</b>			<b>0.025</b>
Mean±SD	4.45±1.107	4.85±0.999	
Median	4.64	4.79	
Range (min-max)	0.17-5.90	1.74-11.45	
<b>Serum magnesium level (mg/dL)</b>			<b>0.0001**</b>
Mean±SD	2.85±1.611	2.09±1.1092	
Median	2.10	1.90	
Range (min-max)	1.09-11.60	0.80-9.36	
<b>Serum calcium-magnesium ratio</b>			<b>0.0001**</b>
Mean±SD	1.94±0.957	1.94±0.957	
Median	2.55	0.21	
Range (min-max)	0.45-6.46	0.06-5.09	

For numerical data, the *P* value was calculated using the unpaired *t* test if the data were normally distributed with the Mann-Whitney test if the data were not normally distributed. *P* value <0.05 is considered statistically significant. \* Indicates that the *P* value was significant.



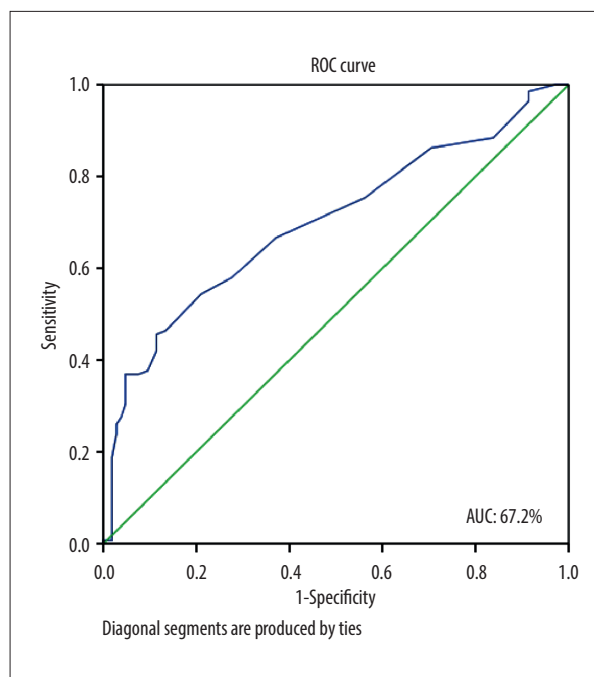
**Figure 1.** The receiver operating characteristics of serum calcium with preeclampsia incidence (area under the curve 58.3%,  $P=0.025$ ).

Patients with preeclampsia demonstrated significantly higher average serum magnesium levels compared with patients without preeclampsia ( $2.85$  vs  $2.09$ ,  $P=0.0001$ ) and the groups had significantly different average serum calcium levels ( $4.45$  vs  $4.85$ ,  $P=0.025$ ) (Table 4).

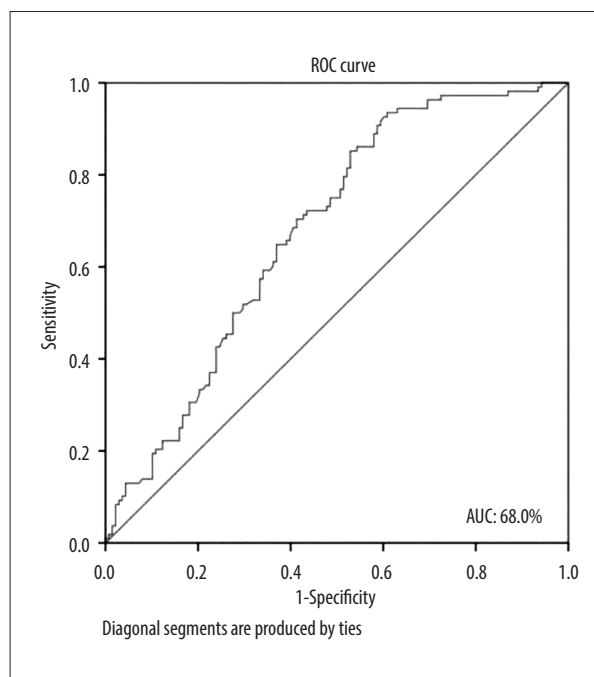
The patients with preeclampsia had a mean serum calcium-magnesium ratio of  $2.54 \pm 0.775$ , which was significantly higher than that of patients without preeclampsia, who had mean serum calcium-magnesium ratio of  $1.94 \pm 0.957$  ( $P=0.0001$ ) (Table 4).

To evaluate the potential diagnostic value of serum calcium for predicting the incidence of preeclampsia, we performed receiver operating characteristic (ROC) curve analysis. The AUC was 58.3% and was significant ( $P=0.025$ ). This result suggested that serum calcium could be used to predict the incidence of preeclampsia accurately in 143 of 246 patients (Figure 1). The cutoff value for serum calcium in this study was 4.65 mg/dL, with a sensitivity of 60.2% and a specificity of 52.9%, which implied that 58.3% of patients with serum calcium levels greater than 4.65 mg/dL were predicted to not have preeclampsia ( $P=0.001$ ).

ROC curve analysis was also performed to evaluate the potential diagnostic value of serum magnesium levels in predicting the incidence of preeclampsia. The AUC was 67.2%, which was significant ( $P=0.0001$ ) and could predict the incidence of



**Figure 2.** The receiver operating characteristics of serum magnesium with preeclampsia incidence (area under the curve 67.2%,  $P=0.0001$ ).



**Figure 3.** The receiver operating characteristics of serum calcium-magnesium ratio with preeclampsia incidence (area under the curve 68.0%,  $P=0.0001$ ).

preeclampsia accurately in 165 of 246 patients (Figure 2). The cutoff value for serum magnesium levels was 1.95 (sensitivity 66.7%, specificity 61.1%). This result indicated that 67.2% of patients with serum magnesium levels greater than 1.95 mg/dL were predicted to have preeclampsia ( $P < 0.001$ ).

ROC curve analysis on the serum calcium-magnesium ratio showed an AUC of 68.0% ( $P = 0.0001$ ). This result suggested that serum calcium-magnesium ratio could be used to predict the incidence of preeclampsia accurately in 167 of 246 patients (Figure 3). The cutoff value chosen was 2.36 (sensitivity 64.8%, specificity 62.3%), which indicated that patients with serum calcium-magnesium ratios of  $< 2.36$  were predicted to have a risk of preeclampsia.

## Discussion

A total of 246 patients were included in this study; 138 patients had preeclampsia and 108 did not have preeclampsia during pregnancy. Our results showed significant differences in parity, body mass index, and nutritional status. These findings are consistent with a study conducted by Lou et al in 2007, which showed that primigravid women had a 2.4-fold higher risk of developing preeclampsia compared with multigravid women [16]. Previous studies have reported that the primigravida state is a risk factor for preeclampsia, which can be related to the fact that primigravida women experience their first exposure to chorionic villi originating from the fetus and maladaptation of the maternal immunological response [17].

A 2-fold increase in free fatty acids and triglycerides was found in patients with preeclampsia compared with patients without preeclampsia in a previous study [18]. One of the determinants in the implementation of the pathophysiology of preeclampsia is diet. The present study found a significant difference in body mass index between patients with and without preeclampsia. Body mass index in our study was measured before delivery. Our results were similar to those of Samur et al in Turkey, who found that preeclampsia is closely related to an increase in body mass index [19].

The present study showed a significant difference in mean serum calcium levels between patients with and without preeclampsia (4.45 vs 4.85,  $P = 0.025$ ). This result is similar to previous studies that found lower blood calcium levels were associated with the incidence of preeclampsia [20]. Darkwa et al, however, found that there was no difference in calcium levels between women with and without preeclampsia [21].

Preeclampsia is a pregnancy disorder that occurs after 20 weeks of gestation and is associated with a new onset of hypertension. In some cases of hypertension with preeclampsia,

symptoms can appear even without protein in the urine. The diagnosis of preeclampsia according to ACOG 2020 is described in Table 3 [22].

The standard range of serum calcium in adult women is 8.5 mg/dL to 10 mg/dL. Pregnant women need an additional elemental calcium intake of about 1.5 g to 2.0 g per day [23]. The present study showed that mean calcium levels in both groups were still below the standard range, which could explain why our study obtained a statistically insignificant result. In addition, we did not examine the patients' calcium intake, so it is not known whether this low calcium level was caused by low intake or other reasons. Moreover, an initial serum calcium level was not examined before preeclampsia was diagnosed. Even so, the group with the highest calcium levels was the group without preeclampsia.

Our study also showed that patients with preeclampsia demonstrated significantly higher average serum magnesium levels than did patients without preeclampsia (2.85 vs 2.09,  $P = 0.0001$ ). In other studies, abnormal magnesium levels in pregnant women in the third trimester were more common in pregnant women with preeclampsia (56.8%) than in those without preeclampsia (35.1%) [24,25]. Nahar et al reported that the estimation of serum magnesium during the antenatal period can help predict preeclampsia and prevent eclampsia [26,27]. Three studies, conducted in 2013, 2018, and 2019, showed that mean calcium levels in patients with preeclampsia were significantly higher than those in patients without preeclampsia [28-30]. There are also some studies that reported no significant differences in serum magnesium levels between women with and without preeclampsia. These differences can be due to differences in study populations and dietary intake. On a systemic level, magnesium can lower blood pressure and change the resistance of peripheral blood vessels [31].

The present study also found that women with preeclampsia had a significantly higher mean serum calcium-magnesium ratio than did women without preeclampsia ( $1.94 \pm 0.957$  vs  $2.54 \pm 0.775$ ;  $P = 0.0001$ ). This finding agrees with a study conducted by Bandebuche et al that showed the mean ratio of calcium-magnesium in the preeclampsia group was lower than that of the non-preeclampsia group [28].

Although the correlation between preeclampsia and levels of calcium and magnesium has been widely studied, there are still little data comparing the ratio between calcium and magnesium in women with and without preeclampsia. A study conducted at a tertiary referral hospital in Nigeria showed that, in a sample of 81 pregnant women, those with preeclampsia had a significantly lower calcium-magnesium ratio than those without preeclampsia [32].

Another study in Ghana conducted at a tertiary hospital showed that patients with preeclampsia ( $n=30$ ) and without preeclampsia ( $n=30$ ) had no significant differences in calcium and magnesium levels or in the ratio of calcium-magnesium [33].

The inverse relationship between calcium intake and hypertensive disorders in pregnancy was first described in the 1980s, based on the observation of Mayan Indians in Guatemala. The women in Guatemala had a low incidence of preeclampsia owing to their high calcium intake, which was due to the traditional method of soaking corn in lime before cooking.

Given the high incidence of preeclampsia and eclampsia, early detection of these conditions is crucial to prevent perinatal morbidity and mortality and to ensure the wellbeing of the mother and baby [5,6]. Changes in electrolyte status have been associated with occurrence of preeclampsia. Electrolytes such as calcium and magnesium make a significant contribution to the proper functioning of vascular smooth muscle cells [18]. A decrease in serum calcium levels and an increase in cellular calcium levels can cause vasoconstriction and increased blood pressure [20]. On the contrary, magnesium acts as a cofactor for enzymes such as sodium-potassium adenosine triphosphatase and is involved in peripheral vasodilation [34].

The ratio of calcium to magnesium plays an important role in the stimulation and transmission of nerve cell signals. A decrease in serum calcium-magnesium ratio can increase excitability and cause burst firing, long-term potentiation, pain transmission, epileptogenesis, and nerve damage [20,35]. This theory was proven by a study that compared the serum calcium-magnesium ratio in patients with preeclampsia and eclampsia. The results showed a significant difference of mean serum calcium-magnesium ratio between patients with preeclampsia and eclampsia ( $4.3\pm 0.92$  vs  $2.93\pm 0.47$ ;  $P=0.000$ ) [7].

The limitations of this study were its single-center design, which may limit the generalizability of the results, and that it included only patients that came to a tertiary teaching hospital in Bandung. Therefore, there was selection bias because the population who came to this facility did not necessarily have similar characteristics to the populations of other health facilities. Nutritional status has a possible impact on

preeclampsia; unfortunately, we did not measure the electrolyte concentrations, hormone levels, and vitamin levels of patients in this study.

## Conclusions

Patients with preeclampsia had a significantly lower serum calcium-magnesium ratio than did patients without preeclampsia; therefore, a low calcium-magnesium ratio could be a risk factor for preeclampsia. Our results also supported that levels of calcium and magnesium are contributory factors in preeclampsia. Finally, we recommend that supplementation of calcium and magnesium can be used as a preventive measure against preeclampsia.

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## Ethical Approval and Consent to Participate

The study was approved by the Research Ethics Committee of Dr. Hasan Sadikin Hospital, Bandung, Indonesia, no LB.02.01/X.6.5/126/2020.

## Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Conflicts of interests

None.

## Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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