

Research Article

Level of Maternal Zinc Serum as Risk Factor of Preeclampsia

Kadar Seng Serum Maternal sebagai Faktor Risiko Preeklamsia

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Abstract

Objective: To investigate the relationship between serum zinc levels and preeclampsia (PE).

Methods: This observational study used case control design. The population of this study was all pregnant women with singleton pregnancy and 28–42 weeks of gestation who were treated at Department of Obstetrics and Gynecology dr. Mohammad Hoesin General Hospital Palembang from August 2020 to November 2020. The study was divided into 2 groups, a case group of 30 pregnant women with PE and a control group of 60 pregnant women without PE. Serum zinc level examination was performed on all samples which met the study criteria. The data was processed by using SPSS software program version 20.0 Windows.

Results: Both case and control groups had no meaningful differences in the general characteristics of the patient. There were significant differences in the maternal serum of average zinc level in both study groups ($p = 0.013$; $43.90 \pm 15.79 \mu\text{g/dL}$). The level of serum zinc which had the best sensitivity and specificity was $45.5 \mu\text{g/dL}$.

Conclusion: There was a meaningful relationship between serum zinc levels and PE. Pregnant women with serum zinc levels $\leq 45.5 \mu\text{g/dL}$ were significantly 3.2 times more risky towards PE than pregnant women with serum zinc levels $> 45.5 \mu\text{g/dL}$. In this case, it was necessary to give zinc earlier in pregnancy to reduce the risk of preeclampsia.

Keywords: case-control study, preeclampsia, zinc.

Abstrak

Tujuan: Mengetahui hubungan antara kadar seng serum dan kejadian preeklamsia (PE).

Metode: Penelitian observasional ini menggunakan desain kasus kontrol. Populasi penelitian ini adalah seluruh ibu hamil dengan kehamilan tunggal dan usia kehamilan 28–42 minggu. Pasien dirawat di KSM/Bagian Obstetri dan Ginekologi RSUP dr. Mohammad Hoesin Palembang dari Agustus 2020 hingga November 2020. Penelitian dibagi menjadi 2 kelompok, kelompok kasus terdiri atas 30 ibu hamil dengan PE dan kelompok kontrol 60 ibu hamil tanpa PE. Pemeriksaan kadar seng serum dilakukan pada semua sampel yang memenuhi kriteria penelitian. Data diolah dengan menggunakan program software SPSS Windows versi 20.0.

Hasil: Tidak terdapat perbedaan yang bermakna mengenai karakteristik umum pasien antara kelompok kasus dan kontrol. Terdapat perbedaan yang signifikan dalam rata-rata kadar seng serum ibu pada kedua kelompok penelitian ($p = 0,013$; $43,90 \pm 15,79 \mu\text{g/dL}$). Kadar seng serum yang memiliki sensitivitas dan spesifisitas terbaik adalah $45,5 \mu\text{g/dL}$.

Kesimpulan: Terdapat hubungan yang bermakna antara kadar seng serum dan PE. Ibu hamil dengan kadar seng serum $\leq 45,5 \mu\text{g/dL}$ secara signifikan berisiko 3,2 kali lebih besar mengalami PE daripada ibu hamil dengan kadar seng serum $> 45,5 \mu\text{g/dL}$. Dalam hal ini, pemberian seng perlu diberikan lebih awal pada kehamilan untuk mengurangi risiko preeklamsia.

Kata kunci: preeklamsia, seng, studi kasus-kontrol.

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INTRODUCTION

Preeclampsia (PE) is defined as gestational hypertension with the presence of proteinuria ≥ 300 mg/24 hours or protein ratio: creatinine ≥ 0.3 or with dipstick (+), or the presence of thrombocytopenia with platelets $< 100,000/\mu\text{L}$, renal insufficiency i.e. creatinine > 1.1 mg/dL, involvement of liver function, serum transaminases increased 2-fold, symptoms of increased intracranial pressure such as dizziness, blurred vision, and seizures.¹ Incidence of preeclampsia varies globally. Based on a secondary analysis of the World Health Association (WHO) Global Survey on Maternal and Perinatal Health in 24 countries in the world, the prevalence of preeclampsia was 10,754 out of 276,388 mothers (4%).

Preeclampsia and eclampsia are significant risk factors for maternal death, perinatal death, premature birth, and low birth weight. Nearly 1 in 10 maternal deaths in Asia and Africa are associated with hypertension in pregnancy. Preeclampsia and eclampsia have the most significant impact on maternal morbidity, mortality, and newborns. Based on the Health Profile of South Sumatra Province in 2019, hypertension in pregnancy was the second most common cause of maternal death at South Sumatra in 2019 with a total of 29 out of 120 maternal deaths.²⁻⁴ Oxidative stress is one of PE etiopathogenesis.¹ Zinc is an essential mineral for many biological functions including protein synthesis, cellular cleavage, nucleic acid metabolism, and one of the trace elements directly involved in oxidative/antioxidant balance. One of the pathogenesis processes in PE that relies heavily on dietary habits and supplements. Some studies have found significantly lower serum zinc levels in PE patients compared with non-PE pregnancies. Serum zinc levels were 43% lower in women with preeclampsia when compared with normal pregnant women in Turkey. Research on Indians found that serum zinc levels in mild and severe preeclampsia women were lower at 12.72 $\mu\text{mol/L}$ in mild preeclampsia and 12.04 $\mu\text{mol/L}$ in severe preeclampsia compared with 15.64 $\mu\text{mol/L}$ in normal pregnancy.⁵⁻⁸ Research related with the benefits of zinc in preeclampsia had not been conducted in Indonesia, especially in dr. Mohammad Hoesin General Hospital Palembang. Because of that, authors are interested in proving the relationship between zinc and preeclampsia in the pregnant women population at dr. Mohammad Hoesin General Hospital Palembang.

METHODS

This study used case-control design to determine the relationship between zinc level in the third trimester pregnant women with preeclampsia and normal pregnancy. This study was conducted at Department of Obstetrics and Gynecology, dr. Mohammad Hoesin General Hospital (RSMH) Palembang from August 2020 to November 2020. The study population was all pregnant women with singleton pregnancy, 28–42 weeks of gestation who were treated at Department of Obstetrics and Gynecology dr. Mohammad Hoesin General Hospital Palembang. Inclusion criteria for the case group are preeclampsia, singleton live fetus, 28–42 weeks of gestation, willing to follow study, and signing informed consent sheet. For the control group, inclusion criteria include 28–42 weeks of gestation, singleton live fetus, getting the same treatment as other normal pregnancies, willing to follow study, and signing informed consent sheet. Exclusion criteria for both groups are pregnancy < 20 weeks of gestation, multiple pregnancies, pregnancy with complications, such as antepartum hemorrhage, liver disease, kidney disease, heart disease, diabetes mellitus, metabolic disorder, intrauterine fetal death, intrauterine growth retardation, and patients who refused to participate in the study. Samples that met the inclusion and exclusion criteria are included in this study. The sample was selected by using consecutive sampling according to the day patient is diagnosed with preeclampsia (time of diagnosis). In the sample, anamnesis, physical examination (vital signs, head to toe), gynecological examination (external and internal examination or according to indication), and additional examination (ultrasound and laboratory examination) in accordance with hospital protocol. Samples that met the study criteria were given informed consent to follow the study. Samples who agreed to participate in the study were randomly grouped into control (non-preeclampsia women) and case (preeclampsia women). All samples were then examined for zinc serum level at Prodia Laboratory, Palembang. Tools and materials needed during the study, both consumable and fix, consisted of tourniquet, stethoscope, weight scale, meter, and Aglient 7700. Consumable kits include 3 cc syringes, trace element blood sample tubes, alcohol swabs, and Randox kits.

All data were captured and tabulated in the

data table and also matched based on age, body mass index (BMI), education level, marital status, obstetric status, socioeconomic level, address, occupation, and maternal disease. We matched demographic variables data (bias variables). Data were obtained in the form of a main table. Tabulation, coding, and calculation of statistical data were performed using SPSS software program version 20.0 Windows. Data analysis would be conducted according to the type of data and data dissemination (Kolgomorov Smirnov test). Chi Square/Fisher's tests were conducted for nominal and categorical data. T-test or Mann Whitney U-test was performed for interval data. The results were presented in the form of tables and graphs with a 95% confidence interval (CI). The successful parameter of this study was the relationship of serum zinc and preeclampsia level with odds ratio of > 2 ($p < 0.05$).

RESULTS

This study was conducted from August 2020 to November 2020 at Department of Obstetrics and Gynecology RSMH Palembang and Prodia Laboratory Palembang. As many as 90 pregnant women met the inclusion criteria. There were 60 samples of PE in the case group and 30 samples in the control group. In this study, the average age of PE patients was 31.23 ± 5.83 years (20 to 41 years of age) and most of them was in the > 30 years (53.3%) group. The average age of patients without PE was slightly younger (29.25 ± 6.77 years (17–44 years of age)) with the most age category was > 30 years (48.3%). Although the average age of patients without PE was slightly younger but the difference was not statistically significant ($p = 0.138$). There was no age category difference between patients with and without PE ($p = 0.266$).

Most of pregnant women with and without PE had high school (90%, 83.3%) education level and were housewives (80%, 85%). Moreover, there were no differences in education ($p = 0.342$) and occupation ($p = 0.319$) between patients with and without PE. Most of patients with PE were overweight (73.3%). There was no BMI difference between patients with and without PE ($p = 0.246$). In addition, the majority of patients with and without PE were 37–42 weeks of gestation (75.9%, 63.3%) and multiparity (43.3%, 43.3%). There was no difference in gestational age ($p = 0.347$) and parity ($p = 0.940$) between patients with and without PE (Table 1).

Table 1. Characteristics of Subjects in the Case and Control Group (n = 90)

Variables	Case group (n= 30)	Control Group (n= 60)	P-value
Age (years)			
Mean \pm SD	31.23 \pm 5.83	29.25 \pm 6.77	0.138 ^a
Median (min–max)	32 (20–41)	30 (17–44)	
Age categories (years old) (%)			
< 20	0 (0.0)	5 (8.3)	0.266 ^b
20–30	14 (46.7)	26 (43.3)	
> 30	16 (53.3)	29 (48.3)	
Education level			
Primary School	1 (3.3)	4 (6.7)	0.342 ^b
Junior High School	2 (6.7)	1 (1.7)	
Senior High School	27 (90.0)	50 (83.3)	
Diploma	0 (0.0)	1 (1.7)	
Bachelor Degree	0 (0.0)	4 (6.7)	
Occupation			
Housewife	24 (80.0)	51 (85.0)	0.319 ^b
Entrepreneur	3 (10.0)	5 (8.3)	
Private employee	2 (6.7)	0 (0.0)	
Civil employee	0 (0.0)	2 (3.3)	
Farmer	1 (3.3)	1 (1.7)	
Student	0 (0.0)	1 (1.7)	
BMI (kg/m²)			
Normoweight	8 (26.7)		
Overweight	22(73.3)	25(41.7)	0.246 ^c
Gestational age, (weeks)			
< 37	7 (24.1)	22 (36.7)	0.347 ^d
37–42	22 (75.9)	38 (63.3)	
Parity			
Nulliparous	9 (30.0)	15 (25.0)	0.940 ^b
Primiparous	7 (23.3)	16 (26.7)	
Multiparous	13 (43.3)	26 (43.3)	
Grand multiparity	1 (3.3)	3 (5.0)	

^aMann Whitney Test, p -value = 0.05

^bPearson Chi Square Test, p -value = 0.05

^cContinuity correction, p -value = 0.05

^dChi Square Test, p -value = 0.05

The mean serum zinc levels in the case and control group were 43.90 ± 15.79 μ g/dL (ranged from 15 to 86 μ g/dL) and 48.77 ± 10.54 μ g/dL (ranged from 22 to 83 μ g/dL), respectively. There was a significant difference in serum zinc level between cases and controls ($p = 0.013$). The serum zinc levels of pregnant women with PE were lower than without PE (Table 2).

Table 2. Serum Zinc Level (n = 90)

Variables	Cases (n= 30)	Controls (n= 60)	P-value
Serum zinc level			
Mean \pm SD	43.90 \pm 15.79	48.77 \pm 10.54	0.013
Median (min–max)	41 (15–86)	49.5 (22–83)	

Mann Whitney Test, $p = 0.05$

DISCUSSION

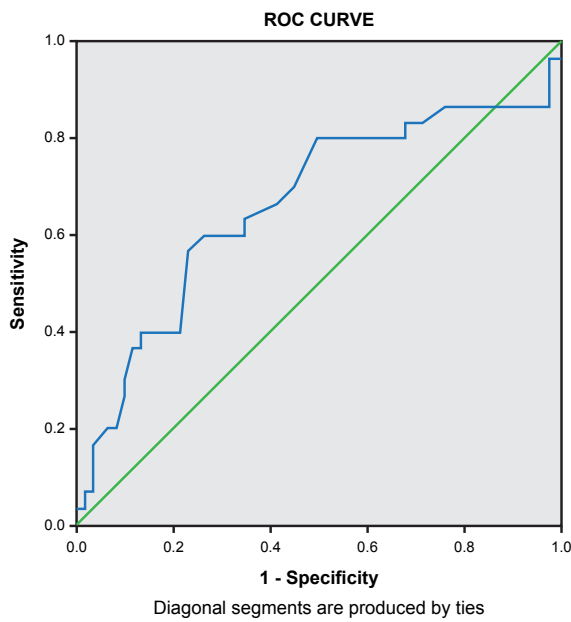


Figure 1. ROC of serum zinc levels

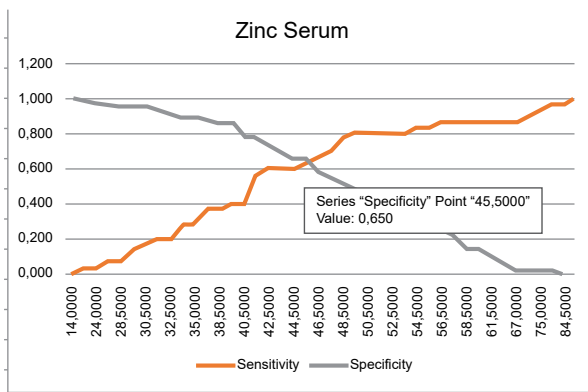


Figure 2. Cut-off curve of sensitivity and specificity of serum zinc level

In the PE group, there were 19 out of 30 people (63.3%) who had serum zinc level ≤ 45.5 $\mu\text{g/dL}$. Meanwhile, in the non-PE group, there were 21 out of 60 people (35%) who had serum zinc level ≤ 45.5 $\mu\text{g/dL}$. There was a significant relationship between serum zinc level and PE. Pregnant women with serum zinc level ≤ 45.5 $\mu\text{g/dL}$ was significantly 3.2 times more risky towards PE than pregnant women with serum zinc levels > 45.5 $\mu\text{g/dL}$ (OR = 3.208 (CI95% 1.288–7.990); $p = 0.020$) (Table 3).

Table 3. The Association between Serum Zinc Level and PE

Characteristic	PE		Total	OR (CI95%)	P-value
	Yes	No			
Serum zinc level ($\mu\text{g/dL}$)					
≤ 45.5	19	21	40	3.208	0.020
> 45.5	11	39	50	(1.288–7.990)	
Total	30	60	90		

Chi Square test, p -value = 0.05

Hypertension in pregnancy is used to describe blood pressure disorders in patients who may only experience an increase in mild blood pressure or severe hypertension with some organ dysfunctions including chronic hypertension, gestational hypertension, superimposed preeclampsia, preeclampsia, eclampsia, and hemolytic syndrome in the form of an increase in liver enzymes and a decrease in the number of platelets (HELLP syndrome).⁹ Severe preeclampsia criteria is when there are one or more symptoms of systolic blood pressure of more than 160 mmHg and diastolic equal to or more than 110 mmHg, proteinuria more than 2 grams/24 hours or +2.¹⁰ Age has an important influence on the incidence of hypertensive disorder in pregnancy. A woman who is 35 years of age or older during pregnancy is defined as "advanced maternal age (AMA)" or "elderly mother".¹¹ Maternal and preeclampsia age relationship form U-shaped curve, the lowest frequency in women aged 25–29 years. Meanwhile, the high frequency was in women with less than 20 years of age and over 35 years.¹² In this study, the average PE patient was 31.23 ± 5.83 years of age (20–41 years) and the majority of patients with age > 30 years was 53.3%. From 95 pregnant women who suffered from PE, the average age was 31.3 ± 5.1 years.¹³ Severe preeclampsia patients had an average age of 31 ± 5.0 years and from 131 preeclampsia patients, the average age was 30.9 ± 5.0 years.^{14,15}

Preeclampsia in morbid obese women increased by 3.97 times. Preeclampsia incidence in obese women with BMI 27.5–30.0 kg/m^2 increased by 3.25 times and preeclampsia incidence in women with BMI 25.0–27.5 kg/m^2 increased by 1.60 times.¹⁶ In this study, PE patients with overweight were 73.3%. The average BMI from 80 PE patients in both treatment groups was 28.0 ± 5.0 kg/m^2 and 27.0 ± 6.0 kg/m^2 .¹² From meta-analysis of 92 studies involving 25,356,688 pregnant women, pregnant women with BMI before pregnant > 30 had 2.8 times risk of preeclampsia (RR = 2.8; CI95% 2.6–3.1).¹⁷ Preeclampsia is often experienced by young and nulliparous women. The incidence of preeclampsia in multiparous women also varies but lower than nulliparous. Nulliparous women are 1.8 times more at risk of preeclampsia compared with primiparous (RR = 1.78; $p = 0.000$).¹⁶ Study reported preeclampsia occurred in 2.7% of nulliparous women and 1.9%

of multiparous women.¹² However, in this study, the majority of PE patients were multiparous (43.3%). Similarly, the majority of PE patients were multiparous (57.1%).¹³

In this study, there were no differences in age, age category, BMI, education, occupation, and parity between groups with and without PE, so both groups were eligible to be compared. Adequate maternal nutrition before and during pregnancy is essential for maternal and child health. Poor nutrition in pregnancy can interfere with maternal and neonatal health. Each year, 3.5 million deaths in women and children are associated with malnutrition.¹⁸ Zinc acts as an intracellular signalling molecule which is capable of communicating between cells by converting extracellular stimuli into intracellular signal and controlling intracellular action. Changes in zinc homeostasis and dysfunction in signal function of zinc can lead to pathogenesis of some diseases. Some studies have shown that lower zinc plasma levels are associated with disruption towards pregnancy outcomes such as fetal malformation, intrauterine growth retardation, preterm birth, preeclampsia, and post partum hemorrhage.¹⁹ Preeclampsia is caused by several factors and associated with an imbalance of increased lipid peroxide (LPO) and decreased antioxidant. Zinc also acts as an antioxidant, so zinc deficiency can cause lipid peroxidation to increase. Several studies have found significantly lower level of serum zinc in preeclampsia patients compared with pregnancies without preeclampsia.⁶ In this study, the average zinc levels of PE patients were 43.90 ± 15.79 mcg/dL (15–86 mcg/dL), significantly lower than patients without preeclampsia which was 48.77 ± 10.54 mcg/dL (22–83 mcg/dL).

There were significant differences in zinc level between pregnant women with preeclampsia and normal pregnancies (902.50 ± 157.15 µgm/L vs 1153.33 ± 67.09 µgm/L; $p < 0.000$).²⁰ Moreover, there were significant differences in zinc level between pregnant women with preeclampsia and control (76.49 ± 17.62 µg/dL vs 100.61 ± 20.12 µg/dL; $p < 0.001$).²¹ In 2010, a study reported significant differences in zinc level between pregnant women with preeclampsia and control (8.6 ± 1.4 µmol/L vs 9.4 ± 0.8 µmol/L; $p < 0.05$).⁹ In addition, there were significant differences in zinc level between pregnant women with preeclampsia and control (0.77 ± 0.05 mg/dL versus 0.98 ± 0.03 mg/dL; $p = 0.000$).²² In this study, there was lower zinc level compared with

other studies. The difference could be caused by the study samples taken at 28–42 weeks of gestation. Meanwhile, the other study took samples from 20 weeks of gestation.

Chemically, zinc has its own uniqueness because it works in regulatory, catalytic, and structural cells that are important in various biological systems. Zinc plays a role in the metabolism of carbohydrate, lipid, and protein as well as the synthesis and degradation of nucleic acid through their role in carbonic anhydrous enzymes (metabolism of CO_2 and HCO_3), thymidin kinase/DNA and RNA polymerase (synthesis of nucleic acids and proteins). Zinc is important for a variety of functions including growth and development, reproductive function, sensory and immune functions, antioxidants, and membrane stabilization.^{23,24} Another important function of zinc is its role in the structure and function of biomemurity. Some researchers have proven that reduced concentrations of zinc in biomemurancy underlie some of the mess associated with zinc deficiency. Zinc becomes an important component of several enzymes that regulate cell growth, protein and DNA synthesis, energy metabolism, gene transcription regulation, hormone level, and growth factor metabolism.^{25,26} In the preconception period, zinc supplementation is used to promote fertility and healthy childbirth. Poor maternal zinc status is associated with fetal malformation, intrauterine growth retardation, preterm birth, preeclampsia, and postpartum hemorrhage.²⁷

Oxidative stress of the placenta is considered an intermediary in the pathogenesis of preeclampsia. There is a lot of evidence to suggest the contribution of oxidative stress to endothelial dysfunction leading to preeclampsia. In human, there are three forms of SOD (Superoxide Dismutases), namely cytosolic Cu/Zn-SOD, mitochondrial Mn SOD and extracellular SOD. Superoxide dismutases are metalloenzymes that catalyze superoxide dismutation into oxygen and hydrogen peroxide molecules and thus form an important part of the cellular antioxidant defense mechanism.²⁸ Increased concentration of oxidative stress markers and decreased antioxidant concentrations in maternal and placental circulation of women with preeclampsia. Increased biomarker lipid peroxidation (MDA) is accompanied by reduced SOD and GPx in cord blood pre-eclampsia and pregnancy eclampsia compared with normal pregnancy. Antioxidant enzyme SOD has been shown to be reduced in

patients with preeclampsia and eclampsia in the same study. Certain substrates and co-factors are necessary for adequate antioxidant enzyme function. Glutathione is a substrate for enzymes that catalyze the reduction of reactive and radical-free oxygen species.²⁸

Zinc is one of the regulators of angiogenesis because it is related to cell proliferation, differentiation and apoptosis.²⁹ Zinc is also a major biomembracy component and is essential for membrane structure and function. Zinc modulates signal transduction in endothelial cells that affect angiogenesis.³⁰ A study proves that zinc has relationship with endothelial dysfunction. Zinc has a membrane stabilizing effect that helps control cell damage due to apoptosis. Some studies have found significantly lower serum zinc level in PE patients compared with patients without PE. By using the ROC, the cut-off point of zinc in preeclampsia is 45.5 mcg/dL. In the PE group, there is 47.5% with zinc level \leq 45.5 mcg/dL while in the non-PE group, there is 22% with zinc levels \leq 45.5 mcg/dL. Pregnant women with zinc level \leq 45.5 mcg/dL have 3.2 times risk of PE compared with pregnant women with zinc levels $>$ 45.5 mcg/dL. Zinc level can be used as a good preeclampsia marker because it obtains an ideal cut-off point to help enforce the diagnosis of preeclampsia.

CONCLUSION

There were significant differences in level of serum zinc between PE and non-PE patients ($p = 0.013$). The level of zinc serum of pregnant women with PE was lower than without PE. Based on the cut-off point curve of serum zinc level, the value that had the best sensitivity and specificity is 45.5 mcg/dL. There was a significant relationship between serum zinc level and PE. Pregnant women with serum zinc level \leq 45.5 mcg/dL were significantly 3.2 times more risky towards PE than pregnant women with serum zinc levels $>$ 45.5 mcg/dL (OR = 3,208 (CI95% 1,288–7,990; $p = 0.020$)). There were no significant differences in the average age, age category, and gestational age. Further study should be conducted to provide zinc supplementation early in pregnancy to reduce the risk of preeclampsia.

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