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Comparison Levels of Copper, Zinc, and Cu/Zn Ratio of in Pre-eclampsia and Normal Pregnancy

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Abstract

BACKGROUND: Pre-eclampsia is a syndrome that occurs in pregnancy, characterized by hypertension, proteinuria, and edema. Zinc and copper are micronutrients that play a role in the performance of several important enzymes in the human body, such as CuZnSOD and ACE2 enzymes that play a role in the pathogenesis of severe pre-eclampsia. Zinc also plays a role in the kallikrein-kinin system in the formation of bradykinin which then acts as a vasodilator.

AIM: This study plans to compare the level of copper (Cu), zinc (Zn), and Cu/Zn ratio in pre-eclamptic and normal pregnancy women.

METHOD: The study recruited 30 pregnant women with severe preeclampsia who were treated at Dr. Hasan Sadikin Bandung and 30 normal pregnant women at one of the Independent Practice Midwives in the Cibabat area, which was conducted in the period September 2021–November 2021. This research was an analytical observational study with a cross-sectional study design. Cu and Zn levels were examined using inductively coupled plasma mass spectrometry (ICP-MS). Chi-square, Student's t-test, Mann–Whitney, and multivariat analysis were used for statistical analysis.

RESULTS: The results of this study showed that the average Cu levels were higher in severe pre-eclampsia (mean: 2.149 vs. 2.116 mol/L, p = 0.728). The median Zn level in the subjects with severe preeclampsia was higher than in normal pregnancies (58 vs. 49 g/dL, p < 0.001). The median Cu/Zn ratio in severe pre-eclampsia subjects was lower than in normal pregnancies (0.034 vs. 0.063 g/dL, p = 0.021).

CONCLUSION: Zn levels were significantly increased in the pre-eclampsia group, Cu levels were not significantly increased in the pre-eclampsia group and the ratio of Cu/Zn levels was significantly decreased in pre-eclampsia group compared to normal pregnancies.

Introduction

Maternal mortality rate (MMR) is the indicator to assess the success of national health efforts. According to the International Classification of Diseases (ICD)-10, the definition of maternal death is maternal death during pregnancy or within 42 days after termination of pregnancy from various causes related to pregnancy and its management, but not due to accidental or incidental causes. MMR is the ratio of maternal deaths per 100,000 live births [1].

The results of the Indonesian Demographic and Health Survey on 2015 stated that the maternal mortality rate (MMR) in Indonesia was still high at 305/100,000 live births. This figure is down when compared to 1991, which was 390 and in 2012, it was 359/100,000 live births. The number of maternal deaths compiled from the recording of family health programs at the Ministry of Health in 2020 showed as many as 4627 maternal deaths in Indonesia with West Java Province contributing the most maternal deaths, 745 maternal deaths. This number shows an increase compared to

2019 at 4221 deaths [2]. The data show that the MMR in 2020 is 230. Despite the decline, the MMR still has not reached the millennium development goals (MDGs) target in 2015 of 102. The target the global sustainable development goals (SDGs) in 2030 is to reduce the MMR to 70/100,000 live births [3], [4].

Problems related to AKI cannot be separated from the various factors that influence it, including maternal health status and readiness for pregnancy, antenatal care, delivery assistance, and immediate postnatal care, as well as sociocultural factors [5]. According to the World Health Organization (WHO), 75% of maternal deaths are caused by bleeding (mostly postpartum hemorrhage), infection, hypertension (pre-eclampsia and eclampsia), complications from childbirth, and unsafe abortion [6]. Based on the causes, the majority of maternal deaths in 2020 in Indonesia were caused by bleeding as many as 1330 cases, hypertension in pregnancy as many as 1110 cases, and disorders of the circulatory system as many as 230 cases [2].

Pre-eclampsia is one of the leading causes of maternal mortality and morbidity. Despite the

enormous polymorphism of the disease, the criteria for preeclampsia have not changed over the past decade (systolic blood pressure >140 mmHg or diastolic blood pressure 90 mmHg and 24-h proteinuria ≥0.3 g). The pathogenesis of preeclampsia has been shown to be related to oxidative stress. Micronutrients such as copper, zinc, magnesium, manganese, and selenium are involved in antioxidant defense which act as enzyme cofactors. Superoxide dismutase (SOD) is an antioxidant enzyme that contains zinc and copper elements [7].

Deficiency of some essential micronutrients may be a predisposing factor in the development of pre-eclampsia because nutrients can modulate oxidative stress by increasing or decreasing free radicals or antioxidants and/or by providing a substrate for free radical formation. Zinc plays an important role in ±300 enzyme functions in the body as a protein cofactor and the preparation of DNA and RNA chains. During pregnancy, the fetus needs zinc in the process of developing its cells. Adequate zinc can prevent babies born prematurely and birth defects. Nutritional intake during pregnancy will greatly affect the outcome of the pregnancy [8].

Copper (Cu) is an essential element found in trace amounts in some cells and tissues, but is most abundant in the liver. The role of Cu is as a cofactor for structural and catalytic purposes of various important enzymes such as cytochrome c oxidase, tyrosinase, p-hydroxyphenyl pyruvate hydrolase, dopamine beta-hydroxylase, lysyl oxidase, and Cu-zinc superoxidase dismutase (Cu,Zn-SOD). High levels of Cu can cause oxidative damage to lipids, proteins, and DNA [9]. Zinc and copper are micronutrients that play a role in the performance of several important enzymes in the human body, such as the enzyme superoxide dismutase (CuZnSOD) and Angiotensin-converting-enzyme 2 (ACE2) which play a role in the pathogenesis of preeclampsia [8]. This study plans to compare the level of copper (Cu), Zinc (Zn), and Cu/Zn ratio in pre-eclamptic and normal pregnancy women.

Materials and Methods

This study is an analytical observational study with a cross-sectional study design to determine the differences in plasma zinc and copper levels between pre-eclampsia with normal pregnancies. The research sample involved pregnant women who had been diagnosed with severe pre-eclampsia in the obstetrics clinic, emergency department (ER), and inpatient ward of the Department of Obstetrics and Gynecology, Dr. Hasan Sadikin Bandung and mothers with normal pregnancies at one of the Independent Practice Midwives in the Cibabat area in the period September 2021–November 2021 who met the inclusion and exclusion criteria.

The inclusion criteria of this study were severe pre-eclampsia patients with gestational age more than 20 weeks and pregnant women in normal condition, without the presence of several conditions such as premature contractions, premature rupture of membranes, antepartum bleeding, and placenta previa, not in labor and fetal growth retardation. While the exclusion criteria in this study were patients with impaired kidney and liver function, vascular and autoimmune disorders such as systemic lupus erythematosus, antiphospholipid stroke syndrome, deep vein thrombosis, chronic diseases such as diabetes mellitus, tuberculosis, chronic kidney failure and hepatitis, taking medication drugs such as diuretics, antilipid drugs (such as cifibrate), glucocorticoid groups (such as dexamethasone and prednisolone), antidepressants, and pre-eclampsia patients who have received $MgSO_4$ therapy.

The determination of the sample size is adjusted to the research objectives and the type of data in the study. In this study, the design used was a non-specific design and the research was unpaired numerical analysis. Using the sample size determination formula for unpaired numerical analytical research, 21 subjects per group were obtained plus 10% to anticipate missing data, so the sample size was 23 per group. Hence, the minimum sample size is 23 people in the pre-eclampsia patient group and 23 people in the normal pregnancy patient group.

Severe pre-eclampsia patients are patients who have a pregnancy of more than 20 weeks with systolic blood pressure >140 and diastolic >90 and have a proteinurine of +1. All patients who meet the inclusion and exclusion criteria will be examined for plasma Zn and Cu levels. Samples were examined in the Prodia laboratory using the inductively couple plasma-mass spectrometer (ICP-MS) method. Process steps in ICP-MS include nebulization, desolvation, vaporization, atomization, and ionization. This examination uses an Agilent 7700. The sample uses plasma (trace element sodium heparin).

The collected data will be processed and analyzed descriptively and analytically. For the descriptive will calculate statistical measures while statistical analysis according to research objectives and research hypotheses. Analysis using Statistical Product and Service Solution (SPSS) for Windows version 25.0. This research has received research ethics approval in accordance with letter number LB.002.01/X.6.5.268/2021 issued by the Research Ethics Committee of Dr. RSUP. Hasan Sadikin Bandung.

Results

The results in Table 1 show the differences in the characteristics of the study subjects between

Table 1: Description of the characteristics of patients with pre-eclampsia and normal pregnancy

Parameter	Pre-eclampsia (*n*=30)	Control (*n*=30)	p
Age (year), mean ± SD	31 ± 6	29 ± 6	0.188[a]
BMI (kg/m^2), mean ± SD	28.9 ± 4.4	23.8 ± 4.0	<0.001[a,*]
Category of BMI, *n* (%)			
< 18.5 (underweight)	0	2 (6.7)	<0.001[c,*]
18.5–25.0 (normal)	7 (24.1)	19 (63.3)	
25.1–27.0 (overweight)	2 (6.9)	5 (16.7)	
> 27.0 (obesity)	20 (69.0)	4 (13.3)	
Weight, mean ± SD	71 ± 13	56 ± 11	<0.001[a,*]
Gestational age (weeks), *n* (%)			
20–28	3 (10.0)	3 (10.0)	1.000[c]
29–33	8 (26.7)	8 (26.7)	
34–40	19 (63.3)	19 (63.3)	
Gravida, *n* (%)			
1	9 (30.0)	9 (30.0)	0.211[c]
2–4	20 (66.7)	16 (53.3)	
> 4	1 (3.3)	5 (16.7)	

Description: Analysis using *t*-test, Mann–Whitney buji, Chi Square cuji, *p < 0.05. BMI: Body mass index, SD: Standard deviation, Description: Analysis using at-test, bMann–Whitney test, cChi Square test.

pre-eclampsia and normal pregnancy. There was no difference in the characteristics of maternal age, gestational age, and number of pregnancies between pre-eclampsia and normal pregnancy (p > 0.05). There was a difference in body mass index (BMI) before pregnancy and body weight between preeclampsia and normal pregnancy (p < 0.05). The pre-eclampsia subject group had the highest BMI, namely, obesity (69.0 %), while the normal pregnancy subject had a normal BMI (63.3%).

Table 2 shows the differences in Zn levels, Cu levels, and Cu/Zn ratios between preeclampsia and normal pregnancy patients. For Cu levels, the results of the normality test showed that the data were normally distributed so that the difference test used was the t-test, while the Zn levels and the Cu/Zn ratio were not normally distributed, so the difference test used was the Mann–Whitney test.

Table 2: The differences in zinc and copper levels between pre-eclampsia and normal pregnancy patients

Variable	Pre-eclapmsia (*n*=30)	Control (*n*=30)	p
Cu plasma level, mean ± SD	2.14 ± 0.43	2.11 ± 0.26	0.728[a]
Zn plasma level, median (minimum–maximum)	58 (33–102)	49 (40–60)	<0.001[b,*]
Cu/Zn plasma, median (minimum–maximum)	0.034 (0.02–0.06)	0.044 (0.03–0.06)	0.021[b,*]

Description: Analysis using [a]t-test, [b]Mann–Whitney test. SD: Standard deviation, Cu: Copper, Zn: Zinc.

The results of the different test showed that there was no significant difference in the mean Cu levels between pre-eclampsia and normal pregnancy subjects (mean: 2.149 vs. 2.116 mol/L, p = 0.728). There was a significant difference in Zn levels and the ratio of Cu/Zn levels between pre-eclampsia and normal pregnancy subjects (p < 0.05). Median Zn levels in pre-eclamptic subjects were higher than in normal pregnancies (58 vs. 49 g/dL, p < 0.001). The median Cu/Zn ratio in pre-eclamptic subjects was lower than in normal pregnancies (0.034 vs. 0.063 g/dL, p = 0.021). From the results of multivariate analysis, it was found that maternal age, weight, and Zn had a risk of pre-eclampsia (Table 3). The greater the mother's age by 1 year, the risk of preeclampsia is 1.175 times, then an increase in body weight of 1 kg will increase the risk of 1.133 times the occurrence of pre-eclampsia, and an increase in zinc levels of 1 g/dL has a risk of 1189 the occurrence of pre-eclampsia.

Discussion

Differences in clinical characteristics of study subjects in patients with pre-eclampsia and normal pregnancy are shown in Table 1. There was no significant difference in the characteristics of maternal age, gestational age, and parity between pre-eclampsia and normal pregnancy (p > 0.05).

In this study, there was a significant difference in BMI and body weight between preeclampsia and normal pregnancy (p ≤ 0.001). There was a difference in BMI before pregnancy and body weight between pre-eclampsia and normal pregnancy (p < 0.05). The pre-eclampsia subject group had the highest BMI, namely, obesity (69.0 %), while the normal pregnancy subject had a normal BMI (63.3%). Obesity is associated with a 2–4-fold increased risk of pre-eclampsia. One study conducted in Tanzania on 17,738 singleton births found 6.6% of mothers were underweight, 62.1% had normal weight, 24% had more BMI, and 7.3% were obese. A total of 582 pregnancies (3.3%) were pregnancies with pre-eclampsia [10].

Table 2 shows the differences in plasma Zn levels, Cu levels, and Cu/Zn ratios between pre-eclampsia and normal pregnancy patients. In this study, it was shown that although the average Cu level in the pre-eclampsia group was higher than in normal pregnancy, it did not show a significant difference (p = 0.728) with the average Cu level between pre-eclampsia subjects (mean: 2.149 mol/L) weight and normal pregnancy (mean: 2.116 mol/L).

Copper is an important element that plays a role in the structure of many enzymes such as lysyl oxidase, cytochrome oxidase, tyrosinase, dopamine-β-hydroxylase, peptidylglycine alpha-amidating monooxygenase, monoamine oxidase, ceruloplasmin, and copper-zinc superoxide dismutase (CuZnSOD). Many different studies have shown that there is an association between the occurrence of pre-eclampsia and this micronutrient. However, several other studies have not shown an association between pre-eclampsia and this micronutrient [11].

One study in Gordan showed a significant or significant difference in copper levels in the pre-eclampsia group compared to normal pregnancies, namely, higher copper levels in the severe pre-eclampsia group [11]. However, other studies conducted by Gayathri *et al.* in India and Serefden *et al.* in Turkey showed lower copper levels in the pre-eclampsia group [12], [13]. Another study that showed no significant difference in copper levels in the pre-eclampsia group compared to normal pregnancy was seen in a study conducted by Elmugabil *et al.* in Sudan [14].

Several mechanisms are known to explain Cu-induced cellular toxicity. Most often is the tendency of free Cu ions to play a role in the formation of reactive

Table 3: Multivariate analysis of copper, zinc and characteristics of age, body weight, and gestational age on pre-eclampsia

Parameter	AOR	95% CI	p
Age (year)	1.175	1.007–1.371	0.040*
Weight (kg)	1.133	1.044–1.229	0.003*
Gestational age (weeks)			
20–28	1 (ref)		
28–34	2.701	0.116–62.77	0.536
34–40	2.481	0.127–48.543	0.549
Cu (μmol/L)	1.301	0.139–12.17	0.817
Zn (μg/dL)	1.189	1.051–1.345	0.006*

Dependent variable: Pre-eclampsia, *Significant p < 0.05. Cu: Copper, Zn: Zinc, AOR: Adjusted odds ratio, CI: Confidence interval.

oxygen species (ROS). Copper in the form of cupric (Cu^{2+}) and cuprous (Cu^+) can play a role in oxidation and reduction reactions. In the presence of superoxide ($^*O^{2-}$) or a reducing agent such as ascorbic acid or GSH (reduced glutathione), Cu^{2+} can be reduced to CU^+, which can then be catalyzed to form hydroxyl radicals ($OH^{\cdot}$) from hydrogen peroxide (H_2O_2). The hydroxyl radical ($OH^{\cdot}$) is the strongest oxidizing radical and can cause reactions to any molecule. Hydroxyl radicals ($OH^{\cdot}$) can initiate oxidative damage by abstracting hydrogen from amino carbons to form protein radicals and from unsaturated fatty acids to form lipid radicals [9].

Impaired organ perfusion is a trigger for oxidative stress, without exception, it also occurs in the placenta. Oxidative stress on the placenta is associated with pregnancy complications such as pre-eclampsia and fetal growth restriction. If not detoxified, these free radicals can damage all surrounding biological molecules including proteins, lipids, and DNA [15].

In this study, there was a significant difference in Zn levels between subjects with pre-eclampsia and normal pregnancy (p < 0.05). Plasma zinc levels in the pre-eclampsia group were found to be higher than in the normal pregnancy group. Median Zn levels in pre-eclamptic subjects were higher than in normal pregnancies (58 vs. 49 g/dL, p < 0.001). The results of this study were the same as those conducted by Mehmet Harma, indicating that there was a significant difference, namely, plasma zinc levels (15.53 vs. 11.93 g/g protein; p < 0.05) which were higher in the preeclampsia group. The same result also occurred in copper levels, there was a significant increase in the pre-eclampsia group (15.53 vs. 11.93 g/g; p < 0.05) [16].

Research conducted by Mehmet Harma found that there was a significant difference in plasma zinc levels (15.53 vs. 11.93 g/g protein; p < 0.05), copper (47.90 vs. 31.60 g/g protein; p = 0.001), and homocysteine (16.39 vs. 9.45) nmol/mL; p ≤ 0.001) in the pre-eclampsia group compared to the normal pregnancy group. Therefore, the study concluded that there was a possible relationship between zinc, copper, and homocysteine levels in the severe pre-eclampsia group [16].

Another study examining the relationship between homocysteine and zinc is seen in a study conducted by Atarod *et al.* at Manzandaran University, Iran. The study showed that there were significant differences between the levels of homocysteine, zinc, copper, and iron between the pre-eclampsia and normal pregnancy groups (p < 0.05) [17]. A systematic review by Luciano *et al.* of 25 studies (a total of 3,649 women) on the relationship between homocysteine and severe pre-eclampsia showed that overall there were higher serum homocysteine levels in pregnant women with pre-eclampsia compared with uncomplicated pregnancies, but the results were heterogeneous (p = 0.12; I^2 = 38.8%). There is no relationship between homocysteine levels and the severity of pre-eclampsia. Mechanisms that explain the occurrence of hyperhomocysteinemia such as folic acid and Vitamin B12 deficiency were not found but markers of oxidative stress and endothelial dysfunction were found to be higher in hyperhomocysteinemia [18].

Homocysteine (Hcy) is one of the essential amino acids formed from methionine, an amino acid containing sulfur. Elevated homocysteine is associated with the development of atherosclerosis and vascular thrombosis. Disturbances in homocysteine-methionine metabolism can cause vascular damage which then causes hypertension which is a clinical manifestation of preeclampsia [19]. Homocysteine plays a role in processes such as fat peroxidation and oxidative stress. Hcy is metabolized by transsulfuration and remethylation pathways. Zn is believed to be involved in regulating homocysteine levels through methionine synthase and betaine homocysteine methyl transferase, both of which are Zn-dependent metallo-enzymes. Therefore, it is believed that Hcy and Zn levels play a role in the risk of severe pre-eclampsia [20].

Several studies that yielded similar results to this study include a study conducted by Eulises Díaz *et al.* in 1998 in Mexico involving 11 women with normal pregnancies and 15 women with severe pre-eclampsia. The study showed that maternal serum zinc levels were higher in the preeclampsia group than in the normal pregnancy group (1.1 vs. 0.99, p = 0.29), while placental zinc levels were found to be lower in the pre-eclampsia group (316 vs. 268) [21]. Research with similar results was also found in a study conducted by Adeniy in Ibadan, Nigeria. It was found that plasma zinc was found to be higher in the severe pre-eclampsia group, while maternal leukocyte zinc levels and placental zinc levels were found to be lower in the pre-eclampsia group than in the normal pregnancy group [22]. Therefore, this study suggests that placental zinc levels are more important than plasma zinc levels because zinc is required in the biosynthesis and maintenance of connective tissue integrity, and a lack of zinc in placental tissue can lead to failure of spiral artery remodeling and atherosclerosis [12].

Several other studies have yielded mixed results on zinc levels in pre-eclampsia. In a study conducted by Gupta *et al.,* it was found that plasma zinc levels were significantly lower in women with pre-eclampsia (9.28 ± 1.63 μmol/L) and eclampsia (9.28 ± 2.61 μmol/L) than the control group (10.63 ± 1.82 μmol/L). No significant difference was found in erythrocyte zinc levels in the

two groups [23]. The function of zinc occurs in cells. However, the status of a person's zinc level is not well reflected by plasma Zn. Zn levels of leukocytes and lymphocytes more reflect a person's Zn status than plasma Zn. However, the examination of Zn levels of lymphocytes and leukocytes requires more complicated isolation and analysis techniques [24]. Plasma Zn levels can be measured using inductively couples plasma mass spectrometry (ICP-MS) [25].

Intracellular and extracellular zinc levels are regulated by zinc transporter proteins. There are two groups of zinc transporter proteins, namely, ZnT and ZIP. ZIP plays a role in delivering Zn^{2+} into the cell cytoplasm and regulating the release of zinc from cell vesicles, thereby reducing plasma zinc levels. Meanwhile, ZnT plays a role in delivering zinc from the cell cytoplasm into intracellular organelles to be carried out of the cell. This transport mechanism helps maintain plasma zinc levels [26]. This explains that in conditions of zinc deficiency as occurs in severe preeclampsia, there has been a release of zinc from intracellular to extracellular, namely to serum/plasma, causing zinc levels in serum or plasma to increase. Therefore, in pre-eclampsia conditions, there has been an intracellular zinc deficiency. This may explain the results of this study, namely, an increase in plasma zinc levels in patients with severe pre-eclampsia.

Another cause that explains the higher Zn levels in the pre-eclampsia group in this study is associated with a significantly increased BMI in this group. It is known that the highest levels of zinc are found in skeletal muscle (63%) and bone skeleton (20%) [26]. This is what causes the Zn levels in the plasma of pre-eclampsia pregnant women in this study to be higher than the group of normal pregnant women. Plasma zinc levels in the control group or the group of normal pregnant women in this study were found to be low, with an average plasma zinc level of 49 ug/dL (range 40-60 ug/dL) with a normal reference value for plasma zinc levels of 60-130 ug/dL. The highest gestational age of the group of normal pregnant women is 34–40 weeks of gestation (63%). This is consistent with the findings in several previous studies that plasma or serum zinc concentrations decreased by 15–35% in late pregnancy compared with pre-pregnancy or early pregnancy concentrations. This decrease in plasma zinc levels is associated with an expansion of plasma volume which increases by about 40% at 30 weeks of gestation. Decreased plasma zinc levels during pregnancy are caused by physiological responses to hemodilution conditions, hormonal changes, increased urinary zinc excretion, increased zinc uptake by maternal tissues, and an active zinc transfer system between mother and fetus. Therefore, pregnant women become more susceptible to Zn deficiency during the third trimester [27], [28], [29].

The results of research by Yasoghara *et al.* showed that zinc levels decreased progressively until gestational age at term, namely, in non-pregnant women 78.1 ± 21.85 g/dL and in pregnant women with gestational age 37 weeks, namely, 60.5 ± 14.42 g/dL. It can be seen that there is a decrease in zinc levels as much as 20% [29].

Low levels of zinc in the control group in this study indicate that there is still a lot of Zn deficiency in pregnant women in Indonesia. It is estimated that half the world's population is at risk of inadequate zinc intake. The prevalence of Zn deficiency in developing countries is very frequent and 61% of the population is at risk of low Zn intake. One study found that 49% of adolescent girls in Delhi and 52% of non-pregnant women in India suffer from Zn deficiency [30]. The study in Bogor city with 114 more than 16 years pregnant women showed most of them (86,8%) had zinc deficiency (serum zinc <0,7 mg/dL) [31].

In this study, there was a significant difference in the ratio of Cu/Zn levels between pre-eclampsia and normal pregnancy subjects (p < 0.05). In this study, the median Cu/Zn ratio in pre-eclamptic subjects was lower than in normal pregnancies (0.034 vs. 0.063 g/dL, p = 0.021). In the state of zinc deficiency, copper absorption will increase. This causes low serum zinc levels, increased serum copper levels, and increased Cu/Zn ratio. Thus, measurement of serum copper can be an additional test to assist in diagnosing zinc deficiency. Several studies have found that the Cu/Zn ratio describes the status of inflammation and oxidative stress better than just looking at the status of zinc and copper alone [32], [33].

In this study, higher Cu levels were found in the pre-eclampsia group compared to the normal pregnancy group (2.149 ± 0.433 vs. 2.116 ± 0.269), although this difference was not significant. With higher Cu levels in the preeclampsia group, it can be assumed that there has been an intracellular zinc deficiency in the pre-eclampsia group although this requires further research. Further research is needed to assess zinc and copper status in the pre-eclampsia group and the normal pregnancy group. In assessing a person's zinc levels, it is necessary to pay attention to dietary history, fasting, sampling time, uniformity of body weight, and BMI of research subjects because plasma/serum zinc levels are influenced by circadian rhythm, fasting, related to mealtime, stress, and a person's BMI. Additional parameters are needed, not only plasma/serum zinc levels, but measuring intracellular zinc levels such as zinc levels in lymphocytes, leukocytes, hair, or baby placenta to determine a person's zinc status. In addition, it is necessary to examine homocysteine levels which can affect plasma zinc levels.

Conclusion

Based on the results of the study, it can be concluded that there is a significant difference in plasma

zinc (Zn) levels and the ratio of plasma copper (Cu) and zinc (Zn) levels in pre-eclampsia patients compared to normal pregnancies. Plasma zinc (Zn) levels were found to be higher in the pre-eclampsia group compared to the normal pregnancy group. Plasma copper (Cu) and zinc (Zn) ratio levels were found to be lower in the pre-eclampsia group than in the normal pregnancy group.

Declarations

Consent to publish

All authors have read and approved the final manuscript.

Availability of data and materials

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

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