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RESEARCH

Differences of Zinc Serum Levels of Heavy Preeclampsia Patients with Normal Pregnancy

Ermawati[1], Hafni Bachtiar[2]

Affiliations *: 1. Obstetrics and Gynecology Department, Faculty of Medicine, Andalas University, Dr. M. Djamil Central General Hospital Padang; 2. Public Health Department, Faculty of Medicine, Andalas University Padang*

Correspondence: *Ermawati, email : erma2812@yahoo.com, Hp: 08116620861*

Abstract

Preeclampsia is a major obstruction complication with increasing incidence and is associated with maternal morbidity and mortality. One theory regarding preeclampsia is the development of oxidative stress due to the benefits of pro-oxidant and anti-oxidant functions that consequently results in free radicals, active oxygen, or reactive nitrogen. The deacrease of Zinc as a cofactor of anti-oxidant enzymes is reported to be associated with an increased risk of preeclampsia. Cross sectional comparative study was conducted in Dr. M. DjamilPadangHospital, SolokDistrict Hospital, PainanDistrict Hospital, BatusangkarDistrict Hospital, and Biomedicallaboratoryof Medical Faculty of Andalas University from September 2014 to February 2015. There were 40 samples with pregnancy beyond 20 weeks which were then divided into two groups; severe preeclampsia and normal pregnancy. Serum zinc wasexamined in both groups. Serum zinc in severe preeclampsia and normal pre-stressed demonstrated a significant difference ($p < 0.05$). The mean concentration of serum zinc in severe preeclampsia and in normal pregnancy were 0.45 ± 0.09 μg / ml and 0.78 ± 0.55 μg / ml with $p = 0.02$. This difference is statistically significant with $p < 0.005$. There was a significant difference between serum zinc concentration in normal pregnant women and that in severe preeclamptic women.

Keywords: *severe preeclampsia, normal pregnancy, zinc serum*

INTRODUCTION

Preeclampsia is a specific pregnancy disease in humans, is defined as a condition of hypertension and proteinuria after 20 weeks gestation. Preeclampsia affects 3% -5% of all pregnancies and is responsible for approximately 60,000 maternal deaths worldwide each year. Preeclampsia is a major pregnancy complication whose incidence is increasing worldwide and is associated with maternal morbidity and mortality.Preeclampsia affects multiorgan including liver, kidney, brain and blood clotting system.[1,2]

The incidence of preeclampsia ranges from 5 - 15% of all pregnancies around the world. At Cipto Mangunkusumo Hospital in Jakarta, 400-500 cases / 4000 - 5000 deliveries / year are found. In Indonesia the incidence rate ranges from 7% - 10%. Research conducted at the hospital. DR. M. Djamil in 1998-2002, the incidence of preeclampsia was 5.5% and eclampsia was 0.88% of 12,034 deliveries. During period 1 January 2005 to 31 December 2007 at BLU (Public service agency) Dr. DR. M. Djamil Padang found 220 patients (4.99%) with severe preeclampsia and 47 eclampsia (1.07%) from 4407 deliveries. From the medical record data

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of patients treated at the Obstetrics and Gynecology Hospital Dr.M.Djamil Padang, in 2010 found 119 cases of 1,287 deliveries (9.2%), during period 1 January to 31 December 2011 found 125 patients with severe cases of preeclampsia (8.31%), eclampsia of the 13 cases, 2 of them died from 1,395 labor. In 2012 there were 140 cases of 1301 deliveries (10.76%).

The most popular theory that describes the pathogenesis of preeclampsia is the 2-stage process, the initial stage is the failure of the maternal spiral arteries in the remodeling process, to adjust to the needs of the fetus. In a normal pregnancy, the syncytiotrophoblast of the placenta invades the vascular lumen wall of the spiral arteries so that the arteries lose the elastic layer of the intima tunica and smooth muscle vascular. Arterial diameter increases to 4-fold compensation for high-capacity, low-resistance and non-responsive blood flow to vasoactive stimulation. This change continues to the third layer of myometrium. But in preeclampsia, the remodeling process is limited to the superficial decidua, and the myometrial segment becomes narrowed and the arterial diameter is narrow. This has become one of the factors that causes that in preeclampsia occurs poor placentation.

In the second stage of the process, the needs of the fetus exceed the supply of uteroplacental, so there is uteroplacental missmatch. If this happens, then many products will be released into the maternal circulation which causes endothelial dysfunction, vasospasm, activation of the coagulation cascade pathway, which ultimately leads to complications in multifunctional organs.

Tissue hypoxia is a source of fat hyperoxidase reactions, whereas the process of hyperoxidase itself requires increased oxygen consumption, so that it will disrupt cell metabolism.5 Fat peroxidase is the result of oxidation of unsaturated fats that produce saturated fat hyperoxidases. Fat peroxidase is a free radical. If the balance between fat peroxidase and antioxidant is disturbed, with peroxidase and oxidants more dominant, then there will be a condition called oxidative stress.

Superoxidation dismutase (SOD) is a metaloenzyme that catalyzes the dismutation of superoxide anions for oxygen and hydrogen peroxide molecules and this is an important part of cellular antioxidants as a defense mechanism. There are 3 forms of superoxidation dismutase, namely cytosol Cu / Zn-SOD, mitochondria MnSOD and extracellular SOD.

Reactive oxygen and reactive nitrogen are normal products of metabolism. Each has a role as a destroyer and useful, both can also be a nuisance or useful for the system of life. Important physiological functions are regulate redx-response signal pathways, including vascular regulation and normal development and growth.

Aerobic organisms can integrate antioxidants to overcome and destroy free radicals. These defenses include antioxidant enzymes (SOD, glutathione peroxidase, catalase) and low molecular antioxidants (vitamins A, C and E, beta-carotene, lipoic acid, glutathione and ubiquinone). Normally, there is a balance between free radicals and free radical scavengers. The danger from biological potential destruction is affected by free radicals from oxidative

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and nitrosative stress. Oxidative stress results from an imbalance between excess oxidants and lack of antioxidant defense mechanisms. Oxidative stress can cause tissue damage which is a pathogenesis of preeclampsia.

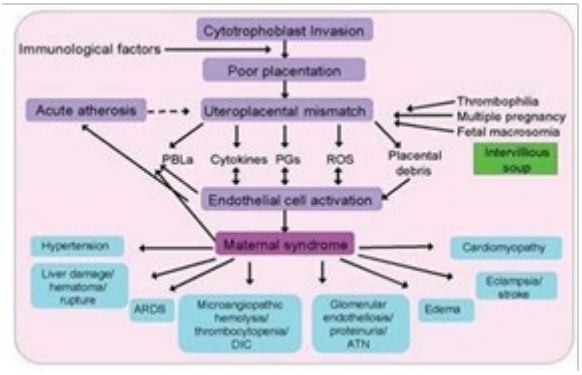

Figure 1. Pathogenesis of Maternal Syndrome in Preeclampsia.[8]

Increased levels of oxidation stress markers and decreased levels of antioxidants in cord blood in pregnant women with preeclampsia and eclampsia are said that oxidative stress markers play an important role as the pathophysiology of preeclampsia and eclampsia. Preeclampsia is associated with oxidative stress in the maternal circulation. The etiology and pathogenesis of pregnancy with preeclampsia is still being debated. Oxidative stress causes clinical endothelial dysfunction precede preeclampsia and its signs and consequences. Low concentrations of mineral elements show that mothers and infants accumulate free radicals. Antioxidant status influences acceptance of oxidative stress. Lots of antioxidants in the body, adequate supplement intake from antioxidant diets is a beneficial role of disease prevention and improving maternal and fetal health

Oxidative stress is known to be an important factor in the pathogenesis of preeclampsia. Antioxidant nutrients such as zinc, iron, and selenium can reduce oxidative stress by free radical scavengers or function as an essential substrate or cofactor for activation of antioxidant enzymes, such as superoxide dismutase (SOD). Ilhan et al showed that serum zinc and SOD levels were significantly decreased while malondialdehyde (a marker of lipid peroxidation) increased in women with preeclampsia compared with normal control groups and healthy pregnant women. These data suggest that SOD, a free radical scavenger, is likely to be consumed by increased lipid peroxidation in preeclampsia and that free radicals may be involved in the pathophysiology of preeclampsia. Zinc status also shows extracellular regulation of superoxidation dismutase, an enzyme that destroys superoxidation radicals, there is a positive correlation between SOD and zinc. Deficiency of the mineral element in preeclampsia is related to the fact that zinc (metallothionein), SOD (copper, zinc, selenium) as a transition metal can catalyze free radical formation because of its role in antioxidant enzymes.

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In previous studies conducted in Korea between 2005 and 2007, 60 people (30 patients with preeclampsia and 30 as controls) were randomly selected among pregnant women who came to the hospital to give birth. Controls are pregnant women who check for pregnancy from the first semester and patients who terminate the pregnancy without complications. The results show that serum zinc in women with serum zinc <13.6 mg / L has a greater risk of developing preeclampsia than in women with serum zinc> 13.6 mg / L.[9]

Kamru et al. Showed that serum zinc levels were 43% lower in women with preeclampsia when compared to normal pregnant women in Turkey. Research on Indians by comparing levels serum zinc in preeclampsia or severe preeclampsia with control. It was found that the serum zinc level in mild preeclampsia and severe preeclampsia was lower at 12.72 µmol / L in mild preeclampsia and 12.04 µmol / L in severe preeclampsia compared with 15.64 µmol / L in normal pregnancy.[7,9]

A cross sectional study was carried out in Bangladesh in 2011. In this study 60 patients were diagnosed with preeclampsia aged 18-39 years, with a gestational age of 20 weeks (group B). To compare age and pregnancy compared with normotensive pregnant women (group A). Past medical history and family history were also recorded, careful examination of diastole and systole. Then a blood test is performed to assess the level of serum zinc in the blood taken in cubiti as much as 5 ml. From in this study, the two groups were matched for age and gestational period, found that SBP (systole blood pressure) and DPB (diastole blood pressure) were higher in group B compared to group A. The mean serum zinc values in group B are lower than those in group A.[10]

Adam et al 2011 reported an increased incidence of preeclampsia and zinc deficiency and it was found that zinc supplementation reduced the high incidence of preeclampsia.[11]

METHOD

This research was conducted with an observational analytic method with a comparative cross-sectional design. This research was conducted on pregnant women who came to the clinic and obstetric emergency room at Dr.M.Djamil Padang Hospital, Batusangkar Regional Hospital, Painan Regional Hospital, RSUDSolok and the examination was carried out at the UNAND FK Biomedical Laboratory in the period September 2014 - February 2015. Research was conducted to determine differences serum zinc levels of patients with severe preeclampsia with normal pregnancy in several hospitals in West Sumatra. The total number of women included in the statistical calculations after the inclusion and exclusion criteria were met was 40 people, who were divided into 2 groups: 20 people at group of patients with severe preeclampsia and 20 people in the normal pregnancy group Statistical analysis to assess significance using the unpaired t test on SPSS 18.0 for windows.

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RESULTS

Basic Characteristics of Research Subjects

The study was conducted from September 2014 to February 2015 with a total of 40 research subjects. The research subjects sampled in the study were divided into 2 groups, 20 patients with severe preeclampsia and 20 patients with normal pregnancies. The basic characteristics of the research subjects are shown in table 1.

Table 1. Basic Characteristics of Research Subjects

Characteristics	Group		p-value
	Normal Pregnancy (mean ± SD)	Severe Preeclampsia (mean ± SD)	
Age	29,30 ± 5,90	30,60 ± 6,62	0,52
Parity	2,15 ± 1,40	2,35 ± 1,63	0,65
Gestasional Age	29,65 ± 3.88	33,40 ± 3,35	0,00
BMI	22,03 ± 1,62	22,83 ± 1,47	0,11

Based on the age characteristics of the respondents in table 4, the mean age value of the group of patients with severe preeclampsia is higher than the average value in the normal pregnancy group obtained (30.60 ± 6.62: 29.30 ± 5.90). This shows that the age difference in patients with severe preeclampsia is equivalent to a normal pregnancy, this can be seen from the p value of 0.52 (p> 0.05).

Based on the characteristics of parity in table 4, the mean parity value in the group of patients with severe preeclampsia was higher than the mean in the normal pregnant group (2.35 ± 1.63: 2.15 ± 1.04). But statistically the difference was not significant. This shows that difference in parity in patients with severe preeclampsia is equivalent to a normal pregnancy, this can be seen from the p value of 0.65 (p> 0.05).

Based on the characteristics of gestational age, the average gestational age of patients with severe preeclampsia is higher than the average gestational age in the normal pregnancy group (33.40 ± 3.35: 29.65 ± 3.88). This shows that there is a significant difference based on gestational age in patients with severe preeclampsia with normal pregnancy, this can be seen from the p value of 0.00 (p <0.05).

Based on the characteristics of BMI (body mass index), the mean BMI value of patients with severe preeclampsia is greater than the mean value of BMI in the normal pregnant group obtained (22.83 ± 1.47: 22.03 ± 1.62). But statistically the difference is not significant. This shows that the difference in BMI in patients with severe preeclampsia is equivalent to a normal pregnancy, this can be seen from the p value of 0.11 (p> 0.05).

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Difference in serum zinc levels in patients with severe preeclampsia and normal pregnancy

Table 2. Differences in serum zinc levels in patients with severe preeclampsia and normal pregnancy

	Normal Pregnancy n = 20	Severe Preeclampsia n = 20	p-value
Mean	0,78	0,45	0,02
SD	0,55	0,09	

From table 2 it can be seen that the mean serum zinc level of patients with severe preeclampsia is lower at 0.45 µgl / mL compared with mean serum zinc levels in normal pregnancy is 0.78 µgl / mL. The results of statistical analysis with the t-test were obtained Significant differences in the mean serum zinc group of patients with severe preeclampsia with the normal pregnancy group, this can be seen from the p value of 0.02 (p <0.05).

DISCUSSION

Maternal age and parity are the most observed risk factors. Uzma Shamsi et al investigated the risk factors for the occurrence of preeclampsia in Pakistan, it was found that the incidence of preeclampsia was mostly found at the age of 19-34 years. Based on the age characteristics, the average age of the group of patients with severe preeclampsia was 30.61 ± 6.62 while the mean value in the normal pregnant group was 29.30 ± 5.90. The results of further statistical analysis, the age difference in patients with severe preeclampsia with normal pregnancy did not have a significant difference, this can be seen from the p value of 0.52 (p> 0.05). Cunningham FG et al stated that the risk of severe preeclampsia was increased in nulliparous compared to multiparous.[5]

In this study based on the characteristics of parity, the mean parity value of the group of severe preeclampsia patients was 2.35 ± 1.63 compared to the average value in the normal pregnant group of 2.15 ± 1.04. The results of further statistical analysis, the difference in parity in patients with severe preeclampsia with normal pregnancy did not have a significant difference, this can be seen from the p value of 0.65 (p> 0.05).

Samples in this study were gestational age over 20 weeks and the average gestational age of the group with severe preeclampsia was 33.4 ± 3.35 compared to the average in the normal pregnancy group of 29.65 ± 3.88. The results of further statistical analysis, the difference in gestational age in patients with severe preeclampsia with normal pregnancy has a significant difference, this can be seen from the p value of 0.00 (p <0.05). The risk of preeclampsia increases with increasing gestational age, according to research by Akolekar Ranjit et al conducted at University College Hospital London. The incidence of preeclampsia is increasing at gestational age above 34 weeks

Body Mass Index (BMI) which is one of the risk factors for preeclampsia. Women with a BMI> 35 kg / m2 have a risk 13.3% compared to women who have a normal BMI.[5] In the study of Akolekar Ranjit et al found an increased risk of the incidence of preeclampsia with

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increasing maternal weight.[13] In this study based on the characteristics of BMI obtained an average of 22.83 ± 1.47 in patients with severe and mean preeclampsia in the normal pregnant group 22.03 ± 1.62. The results of statistical analysis, the difference in BMI in patients with severe preeclampsia with an equivalent normal pregnancy, this can be seen from the p value of 0.11 (p> 0.05).

After analytic samples of patients with severe preeclampsia and normal pregnancy showed that there was a significant difference (p <0.05) of the average serum zinc level in the group of severe preeclampsia patients (0.45 ± 0.09 µg / ml) with the normal pregnancy group (0.78 ± 0.55 µg / ml) which is p = 0.02. Several studies have reported an association between changes in zinc metabolism in preeclampsia and focused on the possible role of micronutrient deficiency as a cause of preeclampsia. This event is more common in developing countries due to lack of intake of essential minerals and multivitamins.

There have not been many studies comparing serum zinc levels in patients with severe preeclampsia with normal pregnancy. Akhtar Selina's research shows an association of zinc deficiency with an increased incidence of preeclampsia. Women with low socioeconomic and women who smoke have a tendency for zinc deficiency. Several studies in different countries observed significantly lower serum zinc levels in women with preeclampsia compared to normal pregnant women.

This is consistent with research conducted in Korea between 2005 and 2007 on 60 people (30 patients with preeclampsia and 30 as controls) were randomly selected among pregnant women who came to the hospital to give birth. Controls are pregnant women who check for pregnancy from the first semester and patients who terminate the pregnancy without complications. The results show that serum zinc in women with serum zinc <13.6 mg / L has a greater risk of developing preeclampsia than in women with serum zinc> 13.6 mg/L.[9]

Kamru et al. Showed that the serum zinc level was 43% lower in women with preeclampsia when compared with normal pregnant women in Turkey. Research in the Indians by comparing serum zinc levels in mild preeclampsia or severe preeclampsia with control, found that zinc serum levels in normal pregnant women was 15.64 µmol / L, in women with mild preeclampsia in 12.72 and in women with severe preeclampsia, 12,04 µmol / L. This shows that serum zinc levels in patients with mild preeclampsia are lower than serum zinc levels in normal pregnant women, and serum zinc levels in severe preeclampsia are lower than those in mild preeclampsia.[7,9]

Although overall serum zinc levels in this study were lower than those in serum studies conducted by Jihye Kim et al, Negi Reena et al and several studies both in the severe preeclampsia group and in the normal pregnant group, this might be due to differences daily food consumption habits in the population and the absence of a standard standard normal serum zinc value in pregnant women.[9]

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In the severe preeclampsia group, the lowest serum zinc was obtained 0.289 µg / ml and the highest is 0.599 µg / ml. High zinc levels were also found in the preeclampsia group. This may be due to the mechanism of preeclampsia that is still unknown and there are many other factors that influence the occurrence of preeclampsia.

In the normal pregnant group also obtained low zinc levels, i.e. 0.450 µg / ml, this may be due to imperfect zinc absorption or it may also be because the preeclampsia condition has not manifested because the gestational age is below 34 weeks and there are still 6 weeks left before term pregnancy. According to research by Akolekar Ranjit et al conducted at University College Hospital London. The incidence of preeclampsia is higher at gestational age above 34 weeks.

This study is in accordance with previous studies by Adam et al 2011 reported an increased incidence of preeclampsia and zinc deficiency and it was found that zinc supplementation reduced the high incidence of this preeclampsia.[11]

In several other studies showed differences in serum zinc levels in patients with severe preeclampsia and normal pregnant women, but statistically the difference was not significant as in the study Altamer et al and Lou Golmohammad et al said the results were not significant, although this study also found zinc levels in preeclampsia were lower than in normal pregnancies. According to the literature low serum zinc is one of the factors increasing the incidence of preeclampsia due to increased oxidative stress but there are still other factors that play a role in increasing oxidative stress and this requires further investigation.[14]

The strength of this study is the finding of a significant mean difference between serum zinc levels in patients with severe preeclampsia and normal pregnancy. This study is in accordance with research conducted in Nigeria in 2010, found that serum zinc in women with severe preeclampsia was lower at 8.6 ± 1.4 µmol / L compared to serum zinc levels in normal pregnant women 9.4 ± 0.8 µmol / L . And this difference is statistically significant with p value <0.05.[11]

The results of this study are also in accordance with research conducted by Akhtar Selina et al in 2011, obtained significantly lower serum zinc levels compared to serum zinc levels in normal pregnant women, 902 ± 157.15 : 1153.33 ± 67.05 with p value <0.001.[10] Weakness in this study is that not all samples are complete laboratory tests and supporting examinations to rule out other risk factors, but this is minimized by exclusion criteria so that other disease factors are expected to be excluded based on a history of illness obtained from the history.

CONCLUSION

The mean serum zinc level in patients with severe preeclampsia was 0.45 ± 0.09 µg / ml, while in normal pregnancy it was 0.78 ± 0.55 µg / ml. There is a significant difference between the serum zinc levels of normal pregnant women and the serum zinc of women in severe preeclampsia.

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