

Research Article

Adiponection Serum Levels in Severe Preeclampsia**Kadar Adiponektin pada Pasien Preeklamsia Berat****Hermie M. M. Tendean, Juneke J. Kaeng, Astrina Supandy**

Department of Obstetrics and Gynecology
Faculty of Medicine Universitas Sam Ratulangi
Prof. dr. R. D. Kandou General Hospital
Manado

Abstract

Objective: To determine the difference adiponection serum levels in pregnant patient with severe preeclampsia and normotency in Manado.

Methods: This study is a cross sectional study which the number of samples obtained was 52 samples in which the sample was divided into 26 pregnant samples with severe preeclampsia and 26 control samples. Samples were taken from Prof. dr. R. D. Kandou Manado Hospital and network hospitals around Manado within the inclusion and exclusion criteria. All patients were explained about the research procedure and signing the informed consent and take a blood sample by using the ELIZA method. After the data is collected, it is entered into the SPSS version 23.0 program for data analysis.

Result: There was a significant relationship between adiponection serum levels with the incidence of severe preeclampsia and normotency. But for body mass index variables there were no significant differences by using T test (independent sample) in each severe preeclampsia and normotency pregnancy group where $p=0.903$. Body mass index, height, weight, and weight gain during pregnancy showed that there is no difference between cases and controls ($p>0.05$) which means that body mass index is not related to the state of the severe preeclampsia and normotency.

Conclusions: There was no relationship between BMI, age, parity, smoking, baby outcomes, delivery method and gestational age with the incidence of severe preeclampsia and normotency against adiponection in this study.

Keywords: adiponection, obstetrics, preeclampsia.

Abstrak

Tujuan: Untuk mengetahui perbedaan kadar adiponektin serum pada pasien hamil preeklamsia berat dengan hamil normal di Kota Manado.

Metode: Studi ini merupakan studi potong lintang. Jumlah Sampel yang didapatkan sebesar 52 sampel dimana sampel dibagi menjadi 26 sampel hamil dengan preeklamsia berat dan 26 sampel kontrol. Sampel diambil dari RSUP Prof. dr. R. D. Kandou Manado dan rumah sakit jejaring sekitar manado yang memenuhi kriteria inklusi dan eksklusi. Semua pasien dijelaskan mengenai prosedur penelitian dan penandatanganan inform consent baru dilakukan pengambilan sampel darah untuk dilakukan pemeriksaan laboratorium dengan menggunakan metode ELISA. Setelah data dikumpulkan, maka dimasukkan ke dalam program SPSS versi 23.0 untuk data analisis.

Hasil: Perhitungan dengan menggunakan uji statistik Mann - Whitney menunjukkan bahwa terdapat perbedaan bermakna nilai rata-rata kadar adiponektin pada pasien hamil normal dengan pasien PEB ($p = 0,000$). Adanya hubungan bermakna kadar adiponektin dengan kejadian preeklamsia berat. Namun untuk variabel IMT yang dilakukan secara uji t (sampel independen) didapatkan kesimpulan tidak terdapat perbedaan bermakna pada masing-masing kelompok normotensi dan kelompok preeklamsia berat di mana $p=0,903$, indeks massa tubuh, tinggi badan, berat badan, serta penambahan berat badan selama kehamilan tidak berbeda antara kasus dan kontrol ($p>0,5$). Ini berarti bahwa IMT tidak berhubungan dengan keadaan terjadinya preeklamsia berat.

Kesimpulan: Tidak didapatkan hubungan antara IMT, usia, paritas, merokok, luaran bayi, cara persalinan dan usia kehamilan dengan kejadian preeklamsia berat dan normotensi terhadap adiponektin pada penelitian ini.

Kata kunci: adiponektin, obstetri, preeklamsia.

Correspondence author. Hermie M. M. Tendean. Department of Obstetrics and Gynecology
Faculty of Medicine Universitas Sam Ratulangi. Manado. hermie-_tendean@yahoo.com

INTRODUCTION

Preeclampsia is a specific condition in pregnancy characterized by placental dysfunction and maternal response to systemic inflammation with endothelial activation and coagulation. Preeclampsia is a clinical syndrome where there is a decrease in organ perfusion due to vasospasm and endothelial activity characterized by hypertension, edema, and proteinuria that arise at gestational age above 20 weeks or immediately after delivery.^{1,2} However, some other women show hypertension accompanied by other multisystem disorders that indicate a severe condition of preeclampsia even though the patient does not have a proteinuria.^{3,4} Frequency of preeclampsia for each country varies due to many factors. In Indonesia is around 3-10% while in developing countries like the United States, it is reported that the incidence of preeclampsia is about 5% of all pregnancies. The World Health Organization (WHO) states that hypertension in pregnancy is a major cause of maternal and fetal mortality and morbidity.^{3,5} About 50.000-70.000 deaths are reported due to preeclampsia. This disease occurs in 3-5% of pregnant women and is a major cause of death of pregnant women. The impact on pregnant women varies from severe hypertension, crisis hypertension, urgency, superimposed preeclampsia, HELLP syndrome, to eclampsia. Maternal Health shows that the incidence rate was 24.7% in 2011, 26.9% in 2012, and 27.1% in 2013 that effect for fetus such as premature birth, stunted fetal growth to fetal death.^{2,6}

Treatment of severe preeclampsia is closely related to the use of antihypertensi. Calcium Channel Blocker acts on arteriolar smooth muscle and cause vasodilatation by inhibiting the entry of calcium into cell. Nifedipin is one of these classes of drugs that have been used since the last decade. The recommended dose is 10 mg orally can be repeated every 15-30 minutes, with a maximum dose of 30mg. Beside nifedipine, the drug used is also nifedipine which is a parenteral calcium that works reduce blood pressure in 20 minutes with 4-6 hours duration. Nifedipine more selectively in myocardial blood vessels, with lower side effect of tachycardia. Furthermore, Magnesium Sulfat prevent seizure in severe preeclampsia. The RCOG guidelines recommend loading magnesium sulphate 4gram for 5-10 minutes followed by a maintenance dose of 1-2 gram/hours for 24 hours postpartum or after

the last seizure but monitoring of urine output, reflex of patella, frequency of breath and oxygen saturation.^{7,8}

Severe Preeclampsia that is not resolved will have an impact on mother and baby. In the mother can occur brain haemorrhage which is the impact of cerebrovascular, neurological disorders, kidney and liver function, pulmonary edema, and blot clotting. While the fetus or baby can fetal growth restriction, preterm labor that can acute respiratory distress until death.^{2,3,9}

Adiponectin is an important adipocytokine secreted mainly by fats that contain adipocytes and plays important role in glucose and lipid metabolism, inflammation and oxidative stress. Changes in adiponectin levels have been shown to directly affect lipid and glucose metabolism which further increase lipid synthesis, free fatty acids, insulin resistance, obesity, cardiovascular disease, type 2 diabetes and inflammatory cytokines. It is a complex and active endocrine organ that plays an important role in regulating lipid and glucose. Adiponectin accounts for about 0.01% of all plasma protein (5-10^{mg}/ml).^{4,5}

Adiponectin as an adipose tissue secretes various proteins into the circulation. These proteins are collectively called adipocytokines which are commonly referred to as adipokines. This adipokine consist of adiponectin, free fatty acid (FFA), leptin, TNF- α , Plasminogen Activator Inhibitor-resistin, bone morphogenic protein, Insulin like growth factor, interleukin-I.^{5,6} Adipose tissue is not only a place to store fat, but also an endocrine organ that plays an important role in the interaction of endocrine, metabolic, and inflammatory signals to regulate the body homeostatic energy. Increase adipose tissue will also be an increase in proinflammatory adipokines secretion along with a decrease in protective adiponectin secretion.

Pathophysiological of preeclampsia concepts related to atherosclerosis, endothelial dysfunction, insulin resistance, and inflammation. Many adipocyte hormones such as tumor necrosis factor, leptin, adiponectin, and interleukin 6 collectively called adiponectin that play an important role in the inflammatory and atherosclerotic processes. It is one of the many specific fatty tissue proteins and expressed and secreted from fat tissue.⁴⁻⁶ In preeclampsia there is an immunological deficiency of trophoblast invasion into the spiral arteries which cause placental hypoperfusion and changes trigger activation of the vascular endothelium.

Experimental and clinical studies have stated that low plasma adiponectin levels are associated with metabolic factors associated with obesity and vascular disease both of which are risk factors for preeclampsia.

METHODS

This study is a cross sectional study to assess the comparison of adiponectin serum level in severe preeclampsia and normotency patients in Obstetrics and Gynecology.

The study was conducted at Prof. dr. R.D. Kandou Hospital Manado, Pancaran Kasih Hospital and Bhayangkara Hospital from Juli 2019 to December 2019.

The population in this study were all women who had clinical symptoms of severe preeclampsia at Prof. dr. R. D. Kandou Hospital and networking hospital in Manado. Samples were selected by history, physical examination and supporting examinations. Samples that met the inclusion criteria and had signed the consent form were included in the study. The sample used by consecutive sampling.

The inclusion criteria was patients with aterm pregnancy which have a high blood pressure and normotency and the ultrasonography study show intrauterine pregnancy in the fields of Obstetrics and Gynecology and willing to participate in research. The exclusion criteria was have a history of diabetes mellitus, cardiac or lung disease, malnutrition, HIV infection, refuse to participate in research, in medicine using antimicrobials, in treatment using immunosuppressants, fetal death, or preterm pregnancy.

The independent variable is severe preeclampsia and normotency patient and the dependent variable is adiponectin serum and body mass index.

Sampling was carried out at patient that met the inclusion criteria. Samples measured weight, height. After that the sample is taken blood sample from the vein about 5cc and has received an explanation and has signed a written statement of consent following the research that has been provided.

Sampling was carried out on blood sampling in patients and was sent to laboratory examination by using the ELIZA method. After the data is collected it is entered into the SPSS version 23.0 program for data analysis.

RESULTS

This research was conducted at Prof. dr. R.D. Kandou Hospital and networking hospital in Manado. The number of samples studied were 52 women who had clinical symptoms of severe preeclampsia and normotency in the field of Obstetrics and Gynecology who met the inclusion criteria.

Table 1 illustrates the distribution of research subjects based on age, gravidity, gestational age, education, BMI, mode of delivery, the history of smoke, occupation.

The highest age distribution in the case of severe preeclampsia and normotency was in the reproductive age group of up to 20 years and below 35 years, 14 people and 15 people (53.8%, 7.6% $p = 0,382$). The results of the distribution of parity where multigravida were more dominant in the severe preeclampsia and normotency were 20 people and 18 people (77%, 69% $p = 0.455$). The results of the distribution of gestational age presentation in the severe preeclampsia group mostly >37 weeks-<40 weeks namely 16 people (61.5%) and for normotency patient were 20 people (77%) ($p=0.542$). The result of the distribution education levels group in severe preeclampsia mostly in primary and junior high school education which 13 people (50%) and normotency woman were 15 people (67%) ($p=0.324$). Moreover, body mass index in the severe preeclampsia group mostly from the overweight and obesity groups of 19 people (75.1%) and normotency of 18 people (69.2%) ($p = 0.451$). The distribution result in group of severe preeclampsia and normotency that show the infant output is about >2500 gram-< 4000gram were 25 people (96.2%) and 24 patient (82.5%) ($p=0.358$). Further more, the results of distribution mother delivery in normotency mostly by vaginal delivery 17 people (65.4%) neither in severe pregnancy by caesarean delivery with 21 people (80%) ($p= 0.435$) In the severe preeclampsia, 17 people (54.4%, $p = 0.358$) were smoke.

Table 2 illustrates the adiponectin serum in normotency and severe preeclampsia. In patient with normotency, adiponectin serum levels mean and standard deviation showed 4.423 ± 1.08 while in severe preeclampsia adiponectin serum level mean and standard deviation showed 2.628 ± 0.477 . The calculation method using the Mann-Whitney statistical test showed that there were significant differences in the average

value of adiponectin serum level in severe preeclampsia ($p=0.000$). There was a significant relationship between adiponectin serum levels with the incidence of severe preeclampsia and normotency.

Table 3 illustrates the distribution of body mass index variable and adiponectin serum in normotency and severe preeclampsia, grouping types of microorganisms. But for body mass index

variables there were no significant differences by using T test (independent sample) in each severe preeclampsia and normotency pregnancy group where $p=0.903$. Body mass index, height, weight, and weight gain during pregnancy showed that there is no difference between cases and controls ($p>0.05$) which means that body mass index is not related to the state of the severe preeclampsia and normotency.

Table 1. Characteristics of Research subjects

Characteristics	Normotency		Severe Preeclampsia		P-value
	N	%	N	%	
Age (years)					0.382
<20	4	15.4	3	11.5	
>20 - <34	15	57.6	14	53.8	
≥ 35	7	27	9	34.7	
Paritas					0.455
Primigravida	8	31	6	23	
Multigravida	18	69	20	77	
Gestational age (week)					0.542
<37	0	0	0	0	
>37 - <40	20	77	16	61.5	
>40	6	23	10	38.5	
Education					0.324
Elementary-Senior High School	15	57	13	50	
Senior High School	6	23	9	34.6	
Bachelor	5	20	4	15.4	
Body Mass Index					0.451
<18.5	0	0	0	0	
>18.5 - ≤ 25	8	30.8	7	26.9	
>25	18	69.2	19	73.1	
Delivery Method					0.435
Normal	17	65.4	5	20	
Cesarean Section	9	34.6	21	80	
History of Smoke					0.358
Never	8	30.8	9	34.6	
Smoker	18	69.2	17	65.4	
Fetal Weight (gram)					0.358
≤ 2500	0	0	2	7.7	
>2500 - <4000	25	96.2	24	92.3	
>4000	1	3.8	0	0	

Table 2. Adiponectin Serum in Normotency and Severe Preeclampsia

Variable	Normotency (n= 26)	Severe Preeclampsia (n=26)	P-value
Adiponectin Level (ng/ml)			
Mean	4.4238	2.6285	
Median	3.9350	2.72	0.000
Std Deviation	1.08555	0.477	
Minimum	3.37	1.74	
Maximum	7.05	3.40	

Table 3. Variable Distribution of Body Mass Index and Adiponectin Serum in Normotency and Severe Preeclampsia

Body Mass Index (BMI)		Adiponectin Serum		
		<3.58 ng/ml	3.58-9.66 ng/ml	>9.66ng/ml
Normotency	<18.5	0	0	0
	>18.5-<25	2	6	0
	>25 (overweight)	3	15	0
Severe Preeclampsia	<18.5	0	0	0
	>18.5-<25	7	0	0
	>25 (overweight)	19	0	0

	Grup	N	Mean	Std. Deviation
IMT	Normal	26	27.8473	4.62196
	PEB	26	27.6900	4.61608

DISCUSSION

In this study, 52 patients were eligible. All subjects of this study have met the inclusion criteria and exclusion criteria and have signed a form of willingness to be involved in this study.

In this study, sample characteristics were assessed from maternal age, education, occupation, and body mass index. In table 1, we can see a comparison of the characteristics of a sample of pregnancy with normotension and severe preeclampsia. The distribution of research subjects according to the age of group of mothers in the study was <20->35 years. The sample distribution in this study based on the age of the mother with the higher percentage in the age group of 20-35 years both in the normotension group of 15 people (57.6%) and the preeclampsia group of 14 people (53.8%). According to the theory that preeclampsia is more often found in the early and late reproductive age, namely in adolescents or over the age of >35 years, but in this study does not fit the theory of the causes of preeclampsia which cause a decrease in adiponectin levels. It is not in accordance with the theory of the factors causing the occurrence of preeclampsia in Prof. dr. R. D. Kandou Hospital and its surroundings based on the age group of 20-35 years.

The highest percentage of parity was multigravida in both normotension and severe preeclampsia groups, this is different from the theory that the frequency of preeclampsia is higher in primigravida compared to multigravida because the formation of antibody inhibitors (blocking antibodies) is not perfect against placental antigens so that arising from an immune response that does not benefit placental histocompatibility and increase the risk of preeclampsia.¹⁰

In this study an analysis show the relationship between serum levels of adiponectin in normotency and preeclampsia, in which there is a significant difference in the level of adiponectin with the average value of adiponectin levels obtained in the normotension group is 39.46 while in the preeclampsia group is 13.54 (p=0.00). This shows the relationship between adiponectin levels and the incidence of preeclampsia. An increased risk of preeclampsia has been noted to be related to several conditions related to insulin resistance, including gestational diabetes, maternal obesity, and excessive weight gain during pregnancy.²

The pathophysiology linking maternal obesity with pregnancy induced preeclampsia is an intensive subject of research with insulin resistance which plays an important role.^{2,6} Although insulin resistance is increased in normal pregnancy activities to facilitate glucose transfer to the fetus and support the rapid growth of the fetus and placenta.

Research reports indicate that insulin signals and angiogenesis are closely related and irregularities in angiogenesis and insulin resistance can cause change in cellular critical function, endothelial cell injury, and consequently an increased risk for preeclampsia.

In this study table 3 shows that there is no relationship between the value of body mass index with the incidence of preeclampsia and the average body mass index in normotensive pregnancy is 27.84 and there is a decrease in the average body mass index value in the preeclampsia group 27.69 with a p-value 0.903. At the Hutzell-Wayne University Hospital in 22 normotensive pregnant women and 77 preeclampsia women showed that there was decrease in adiponectin levels with increasing maternal body mass index. Adiponectin levels in

the weight preeclampsia group with overweight and obesity (BMI>25kg/m²) were lower than the weight preeclampsia group with normal weight. Women with preeclampsia also had a higher BMI compared to normotensive control. This is because in obese there is an increase in inflammatory mediating factors such as IL6, C reactive peptide, TNF-alpha, and macrophages from the placenta which can cause dysfunction in the endothelial and vascular. But in this study, the adiponectin correlation test with BMI showed a weak correlation^{5,6}

CONCLUSION

From the results of this study it was found that adiponectin levels in severe preeclampsia were significantly lower compared to normotensive pregnancy so it can be concluded that adiponectin levels were associated with the incidence of severe preeclampsia.

SUGGESTION

Further research to assess the relationship of adiponectin, preeclampsia, body mass index using a large sample and not only for aterm pregnancy but continue by examining the adiponectin levels in first/second trimester pregnant women as predictor of preeclampsia. Serum adiponectin examination can be considered as a marker for preeclampsia.

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