Acta Scientific Women's Health (ISSN: 2582-3205)

Volume 4 Issue 7 July 2022

Research Article

The Relationship Between Leptin Levels and the Leptin Gene Promoter Polymorphism G-2548A at the Onset of Preeclampsia

Roza Sriyanti[1]*, Masrul[2], Johanes C Mose[3] and Netti Suharti[4]

[1]Division of Maternal - Fetal Medicine, Department of Obstetrics and Gynecology, Faculty of Medicine, Andalas University/Dr. M. Djamil Central General Hospital, Padang, Indonesia

[2]Department of Nutrition, Andalas University, Padang, Indonesia

[3]Division of Maternal - Fetal Medicine, Department of Obstetrics and Gynecology, Faculty of Medicine, Padjadjaran University/Hasan, Sadikin, Bandung, Indonesia

[4]Department of Microbiology, Andalas University, Padang, Indonesia

***Corresponding Author:** Roza Sriyanti, Division of Maternal - Fetal Medicine, Department of Obstetrics and Gynecology, Faculty of Medicine, Andalas University/ Dr. M. Djamil Central General Hospital, Padang, Indonesia.

DOI: 10.31080/ASWH.2022.04.0399

Received: April 14, 2022

Published: June 28, 2022

Abstract

Introduction: Preeclampsia is one of the complications of pregnancy that often increases maternal morbidity and mortality. The influence of the leptin gene promoter polymorphism G-2548A plays a role in the development of preeclampsia.

Objective: This study was to determine the relationship between leptin levels and the leptin gene promoter polymorphism G-2548A at the onset of preeclampsia.

Methods: This study used a cross sectional comparative study design which was conducted from May 2018 - April 2019 in the Obstetrics and Gynecology section/SMF of General Hospital Dr. M. Djamil Padang, Achmad Mochtar Hospital, Solok Hospital, Reksodiwiryo Hospital. Sampling with consecutive sampling consisting of 69 pregnant women met the inclusion and exclusion criteria. Examination of the promoter polymorphism of the G-2548A leptin gene was carried out by sequencing method.

Results: From the results of the study, the highest leptin levels were found in EOPE compared to LOPE and normal pregnancies. In EOPE, the highest leptin levels were found in the AA genotype (52.81 ± 66.14), in LOPE it was found in the GG genotype (47.40 ± 44.29), and in normal pregnancy the highest leptin levels were found in the AA genotype (18.78 ± 29.75).

Conclusion: There was no significant relationship between leptin levels and the leptin gene promoter polymorphism G-2548A at the onset of preeclampsia.

Keywords: Early Onset Preeclampsia; Leptin Levels; Leptin Gene Promoter Polymorphism

Abbreviations

EOPE: Early Onset Preeclampsia; LOPE: Late Onset Preeclampsia; FGR: Fetal Growth Restriction; SLR: Soluble Leptin Receptors; LEPR: Leptin Receptor; SNP: Single Nucleotide Polymorphism; BMI: Body Mass Index

Introduction

Preeclampsia is a multisystem disorder that occurs in about 2-10% of all pregnancies and most often causes maternal and fetal morbidity and mortality [1,2]. The World Health Organization

(WHO) reports 16% of maternal mortality caused by preeclampsia in developing countries [3]. Preeclampsia can be divided into sub classifications: early onset preeclampsia (EOPE) and late onset preeclampsia (LOPE). The risk of maternal and fetal mortality in early onset preeclampsia (EOPE) is significantly greater than that of late onset preeclampsia (LOPE), this is due to the large majority of problems with severe placental perfusion and prematurity [4]. Most newborns from EOPE pregnancies experience premature and fetal growth restriction (FGR) [5,6].

EOPE occurs in 5-20% of all cases of preeclampsia related to impaired fetal growth, fetal pathology, impaired uterine blood circulation, small placental size, preterm birth, and neonatal mortality and morbidity. While LOPE is about 75-80% of the total cases of preeclampsia related to maternal morbidity (such as metabolic syndrome, impaired glucose tolerance, obesity, dyslipidemia, chronic hypertension), with normal fetal weight and normal placental volume [7]. Abnormalities in the placenta are undoubtedly the pathogenesis of preeclampsia. The presence of abnormal placentation including incomplete trophoblastic spiral artery invasion plays an important role in the pathogenesis and pathophysiology of preeclampsia [1,8].

Reduced placental perfusion will produce fetal-placental signals that affect maternal metabolism and physiology that will affect the course of nutrition and fetal growth. If pregnant women cannot tolerate these signals, it will cause preeclampsia. One of the signals of pregnancy is the hormone leptin. The increased leptin hormone can stimulate the placental leptin gene in trophoblast cells. Accompanied by an increase in soluble leptin receptors (SLR) in the cytotrophoblast layer of the placenta. Polymorphisms of the leptin gene and the leptin receptor (LEPR) can increase circulating leptin expression. The leptin gene and the LEPR gene have been identified in humans and are located on chromosome 7q31.3 and chromosome 1p31. The single nucleotide polymorphism (SNP) of the leptin gene G-2548A is associated with one of the most common leptin gene polymorphisms [5].

The leptin gene polymorphism G-2548A occurs in the promoter gene and there is a substitution of glutamine to adenine at nucleotide 2548 in region 5. Recent studies in Turkey showed that the polymorphism of the leptin G-2548A gene, both genotypes AA and GA and GG, was a predictor of increased leptin and BMI. Sugathadasa., *et al*. (2010) in their research, showed that preeclampsia in pregnancy was associated with higher circulating leptin, lower SLR levels and with leptin gene polymorphism G-2548A genotype AA. Vasku., *et al*. (2008) did not find a significant relationship between G-2548A leptin gene polymorphisms with preeclampsia and normal pregnancy [9].

There is still little research on the relationship between leptin levels and the leptin gene polymorphism G-2548A in preeclampsia, especially in EOPE, where not many studies have been conducted and the results are controversial. The purpose of this study was to evaluate the relationship between leptin levels and the leptin gene polymorphism G-2548A in preeclampsia, especially in EOPE [9].

Materials and Methods

Subjects

The study was conducted at Dr. Hospital. M. Djamil Padang, network hospitals and health centers. The study used a cross-sectional comparative study design by comparing the three study groups, namely early onset preeclampsia, late onset preeclampsia, and normal pregnancy to evaluated leptin levels with the leptin gene promoter polymorphism G-2548A at onset of preeclampsia. Preeclampsia is defined as hypertension with minimum criteria for systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg after 20 weeks' gestation, and one or more proteinuria ≥ 300 mg/24 hours or urine/creatinine protein ratio ≥ 30 mg/dl (1+ urine dipstick), renal insufficiency, hematological abnormalities, liver disorders, cerebral disorders, pulmonary edema. the number of samples was 69 samples that met the inclusion criteria (single pregnancy women, gestational age > 20 weeks, there were no severe medical abnormalities, no chorioamnionitis and no pregnancy with major congenital abnormalities), and exclusion criteria damage to blood samples during the research process, and patients drop out during the research process). The study was conducted at Dr. Hospital. M. Djamil Padang, network hospitals and health centers.

Samples

Patients who meet the inclusion and exclusion criteria will be interviewed to obtain characteristic data including name, age, identity number, address, contact number, history of pregnancy, first day of the last day or ultrasound examination to assess gestational age.

After the patient signed a letter of informed consent, venous blood specimens were collected in the mediana cubital vein by

folding the elbow by 10 ml. Next blood is sent to the laboratory for examination HIF-1α levels, leptin levels and leptin gene promoter polymorphism G-2548A.

Statistical analysis

Data consisted of leptin levels and the genotype of the leptin gene promoter G-2548A in preeclampsia. Categorical data is presented in terms of frequency, while continuous data is presented in terms of mean/median and standard deviation/minimum-maximum range. Prior to the bivariate analysis, the data normality test was conducted using the Saphiro Wilk test. The results of the Saphiro Wilk test are said to be normally distributed if the p value > 0.05. If the data is not normally distributed, then a non-parametric test is performed.

Results and Discussion

Results

The study was conducted on 69 patients consisting of 23 early onset preeclampsia, 23 late onset preeclampsia and 23 normal pregnancies. Sample characteristic of 69 patients, based on age, gestational age, parity, sistole and diastole blood pressure, body mass index (BMI), and birth weight was shown in table 1.

Characteristic	EOPE (n = 23)	LOPE (n = 23)	Normal (n = 23)
Age of pregnant women (years)	32.35 ± 7.33	32.96 ± 6.8	29.30 ± 2.18
Gestational age (week)	29.04 ± 3.37	36.91 ± 2.04	38.22 ± 0.67
Parity (%) Nullipara Multypara	 34.8 65.2	 39.1 60.9	 4.3 95.7
Systolic blood pressure (mmHg)	169.35 ± 20.90	160.43 ± 17.18	114.78 ± 4.87
Diastolic blood pressure (mmHg)	103.61 ± 12.32	100 ± ,9.53	73.38 ± 4.87
BMI before pregnancy (kg/m^2)	28.52 ± 5.06	28.76 ± 6.04	25.08 ± 1.69
BMI during pregnancy (kg/m^2)	32.18 ± 4.84	35.10 ± 675.76	31.02 ± 1.96
Birth weigtt (gr)	1363.48 ± 486.58	294.00 ± 675.76	2730.43 ± 186.92

Table 1: Clinical characteristics of the study population.

Based on the table it is known that early onset and late onset preeclampsia have respondents with almost the same age, namely 32 years, whereas in normal pregnancies the average age is 29 years. In the early onset preeclampsia group the systolic blood pressure is higher than the late onset preeclampsia and normal pregnancy (169,35 ± 20,90 mmHg vs 160,43 ± 17,18 mmHg vs 114,78 ± 5,11 mmHg). Likewise with diastole blood pressure found in the preeclampsia group early onset is higher than late onset preeclampsia and normal pregnancy (103,61 ± 12,32 mmHg vs 100 ± 9,53 mmHg vs 73,48 ± 4,87 mmHg). In the late onset preeclampsia group, the mean BMI before pregnancy was higher than that of early onset and normal pregnancy (28,76 ± 6,04 kg/m^2 vs 28,52 ± 5,06 kg/m^2 vs 25,08 ± 1,69 kg/m^2). Similar results were found in BMI during pregnancy (35,10 ± 6,56 kg/m^2 vs 32,18 ± 4,84 kg/m^2 vs 31,02 ± 1,96 kg/m^2).

	EOPE			
	GG	GA	AA	p value
Leptin (ng/ml)	51.80 ± 72.03	105.41 ± 113.38	52.81 ± 66.14	0,430
	LOPE			
	GG	GA	AA	p value
Leptin (ng/ml)	47.40 ± 44.29	28.92 ± 38.42	25.71 ± 24.00	0.518
	Normal pregnancy			
	GG	GA	AA	P value
Leptin (ng/ml)	5.22 ± 3.04	17.86 ± 23.01	18.78 ± 29.75	0.706

Table 2: The relationship between leptin levels and the promoter polymorphism of the G-2548A leptin gene on the onset of preeclampsia.

The statistical results in table 2 shows that the highest leptin levels were found in EOPE compared to LOPE and normal pregnancies. In EOPE, the highest leptin levels were found in the AA genotype (52.81 ± 66.14), in LOPE it was found in the GG genotype (47.40 ± 44.29), and in normal pregnancy the highest leptin levels were found in the AA genotype (18.78 ± 29.75).

From the results of the study, based on statistical tests, there was no significant relationship between the leptin gene promoter polymorphism G-2548A and leptin levels ($p > 0.05$).

Discussion

From the results of the study, it was found that the highest levels of leptin in the GA genotype, GG genotype, and AA genotype polymorphisms were found in EOPE compared to LOPE and normal pregnancy. When tested statistically, it turns out that in each group there is no significant relationship ($p > 0.05$). the presence of polymorphisms of the leptin gene and the leptin receptor (LEPR) is thought to increTse circulating leptin expression. A research found that the leptin gene polymorphism G2548A is associated with the expression and function of the leptin gene which appears to have an important influence on blood pressure during pregnancy [10-12].

The relationship of the LEP G-2548A polymorphism with serum leptin levels in other populations has been widely studied but the results are still controversial. The preeclampsia group, the lowest leptin levels were found in the AA genotype and the highest in the GG genotype, and there was no statistically significant relationship [9].

Polymorphisms in the promoter region of the leptin gene most often affect gene expression and adipose tissue secretion of leptin, possibly at the transcriptional level. These findings suggest that, in addition to hormonal factors, sequence variations in the leptin gene may explain the interindividual differences in circulating leptin levels observed in subjects with certain levels of body fat. Differences in the results of several studies may be caused by differences in genetic background and environmental conditions, different inclusion criteria, number of population samples, diagnostic criteria, differences in target populations and differences in blood collection time, confounding factors, background ethnic differences in the population can also be reasons. on this variation [13].

In this study, there was no relationship between the G-2548A polymorphism and the onset of preeclampsia due to the possibility that the G-2548A polymorphism had a length of 419 bp, while the length of the leptin gene was 20 kb, so there is a possibility of other leptin gene polymorphisms associated with preeclampsia. The G-2548A polymorphism did not alter the transcriptional regulatory site in the promoter region of the leptin gene. This does not rule out the possibility that the polymorphism has a disequilibrium relationship with other regulations that have not been unified. This indicates that the polymorphism can indeed modify the transcriptional rate of the leptin gene. The description of transcription factors affecting the G-2548 polymorphic site needs further evaluation.

Conclusion

The relationship between leptin levels and the leptin gene promoter polymorphism G-2548A at the onset of preeclampsia showed that the highest leptin levels were found in the AA genotype in EOPE with a total of 52.81 ± 66.14. Based on statistical tests, there was no significant relationship between the leptin gene promoter polymorphism G-2548A and leptin levels ($p > 0.05$).

Conflict of Interest

The authors declare no conflict of interest.

Bibliography

1. Rigó Jr János., *et al*. "Leptin receptor gene polymorphisms in severely pre-eclamptic women". *Gynecological Endocrinology* 22.9 (2006): 521-525.

2. Salimi Saeedeh., *et al*. "Different profile of serum leptin between early onset and late onset preeclampsia". *Disease Markers* 2014 (2014).

3. Cunningham F Gary., *et al*. "Hypertensive disorders". *Williams obstetrics* 24 (2014): 728-9.

4. MacKay Andrea P., *et al*. "Pregnancy-related mortality from preeclampsia and eclampsia". *Obstetrics and Gynecology* 97.4 (2001): 533-538.

5. Von Dadelszen., *et al*. "Subclassification of preeclampsia". *Hypertension in Pregnancy* 22.2 (2003): 143-148.

6. Ogge Giovanna., *et al*. "Placental lesions associated with maternal under perfusion are more frequent in early-onset than in late-onset preeclampsia". *Journal of Perinatal Medicine* 39.6 (2011): 641-652.

7. Van der Merwe JL., *et al*. "Are early and late preeclampsia distinct subclasses of the disease—what does the placenta reveal?". *Hypertension in Pregnancy* 29.4 (2010): 457-467.

8. Sulistyowati Sri. "Early and late onset preeclamsia: What did really matter". *Journal of Gynecology Women's Health* 5.4 (2017): 555670.

9. Sugathadasa B H K R., *et al*. "Association of–2548 G/A Polymorphism in the Leptin Gene with Preeclampsia/ Pregnancy-Induced Hypertension". *Hypertension in Pregnancy* 29.4 (2010): 366-374.

10. Bienertová-Vašků Julie., *et al*. "Is there any link between severe pre-eclampsia and defined polymorphisms in leptin and adiponectin genes?". *Journal of Obstetrics and Gynaecology Research* 34.5 (2008): 858-864.

11. Carrillo-Vazquez Jonathan P., *et al*. "G-2548A leptin promoter and Q223R leptin receptor polymorphisms in obese Mexican subjects". *American journal of agricultural and biological science* (2013): 34-43.

12. Farias Dayana R., *et al*. "Polymorphisms of leptin (G2548A) and leptin receptor (Q223R and K109R) genes and blood pressure during pregnancy and the postpartum period: a cohort". *American Journal of Hypertension* 30.2 (2017): 130-140.

13. Liu Y., *et al*. "Role of leptin receptor gene polymorphisms in susceptibility to the development of essential hypertension: a case–control association study in a Northern Han Chinese population". *Journal of Human Hypertension* 28.9 (2014): 551-556.