Research Article

Hypoxia Inducible Factor-1α in Correlation with Preeclampsia

Hubungan Kadar Hypoxia Inducible Factor-1α dengan Preeklamsia

Hendrik Juarsa, Hermie M M Tendean, John E Wantania

Department of Obstetrics and Gynecology
Faculty of Medicine University of Sam Ratulangi/
Prof. Dr. R. D. Kandou
Manado

Abstract

Objective: To know the correlation between Hypoxia Inducible Factor (HIF)-1α level with preeclampsia.

Method: The study was conducted at the Obstetrics and Gynecology Department of Prof. Dr. R. D. Kandou Hospital. This research was carried out from April to June 2014. This study is a cross-sectional analytic approach in preeclampsia and normotensive pregnancy. We perform cubital venous blood sampling for inspection by 5 ml of serum and stored it in a refrigerator (-20°C). The level of HIF-1α serum was done by quantitative ELISA method in Prodia Lab Jakarta.

Result: Seventy six pregnant women with 38 normotensive pregnancies and 38 preeclampsia, showed a significant association between the average levels of HIF-1α in the serum of pregnant women with preeclampsia compared to normotensive pregnancies (p = 0.000).

Conclusion: There is a positive relationship between the levels of HIF-1α in serum of preeclampsia, in which HIF-1α levels in preeclampsia was higher than normotensive pregnancies.

[Indones J Obstet Gynecol 2016; 1: 19-22]

Keywords: hypoxia inducible factor-1α, preeclampsia

Abstrak

***Tujuan**: Mengetahui kadar HIF-1α serum pada preeklamsia.*

***Metode**: Penelitian dilakukan di bagian Obstetri dan Ginekologi RSUP Prof. Dr. R. D. Kandou. Penelitan ini dikerjakan mulai bulan April sampai Juni 2014. Penelitian ini merupakan penelitian analitik menggunakan pendekatan potong lintang pada preeklamsia dan kehamilan normotensi. Dilakukan pengambilan darah vena cubiti sebanyak 5ml untuk pemeriksaan serum dan disimpan dalam lemari es (-20°C). Pemeriksaan kadar HIF-1α serum dilakukan dengan cara kuantitatif, menggunakan metode ELISA.*

***Hasil**: Tujuh puluh enam perempuan hamil dengan 38 orang dengan kehamilan normotensi dan 38 orang dengan preeklamsia. Didapatkan hasil hubungan yang bermakna antara kadar rata-rata HIF-1α serum dalam ibu hamil preeklamsia dibandingkan dengan kehamilan normotensi (p = 0,000).*

***Kesimpulan**: Terdapat hubungan positif antara kadar HIF-1α serum pada preeklamsia, di mana kadar HIF-1α pada preeklamsia lebih tinggi secara signifikan dibandingkan kehamilan normotensi.*

[Maj Obstet Ginekol Indones 2016; 1: 19-22]

***Kata kunci**: hypoxia inducible factor-1α, preeklamsia*

Correspondence: Hendrik Juarsa. Perumahan Griya Pantai Malalayang no. 12A Manado. Telephone: 082193290088. email: hendrikjuarsa@hotmail.com

INTRODUCTION

The incidence of preeclampsia varies greatly from country to country.[1] Preeclampsia is a multisystem disorder that complicated at 3% - 8% of pregnancies in Western countries and is a major source of morbidity and mortality in the world.[2] Meanwhile, the prevalence of hypertension in Indonesia were obtained through measurements at age > 18 years was 25.8%.[3] Overall, 10% -15% of maternal deaths are directly related to the preeclampsia. Some epidemiological study support the hypothesis of genetic and immunological as the cause of preeclampsia.[4]

Until now, there has not been an ideal way to be able to predict the occurrence of preeclampsia at an early stage. This is due to the etiology and definitive pathogenesis of preeclampsia remains unclear, so that preeclampsia is still referred to as the disease of theories.[5]

In the early preeclampsia, there is a failure of cytotrophoblast invasion into the maternal spiral arteries. This will cause a decrease in uteroplacental perfusion that followed by the failure of the unit of fetoplasenta to get enough oxygen from the intervillus space that ultimately lead to a state of hypoxia in the placenta resulting in the release of a factor which so-called Hypoxia Inducible Factors (HIF). It is necessary to spur more cytotrophoblast cells to migrate into cytotrophoblast extravillus that will become invasive cytotrophoblast who will invade vascular endothelial, deeper into the spiral arteries. The entire process from the placenta to ensure adequate oxygen supply to the developing fetus during pregnancy.[6]

HIF-1α levels in preeclampsia is still not widely studied. If the levels of HIF-1α is known related to preeclampsia, it can be done as early as possible so the anticipation can reduce the morbidity and mortality of the mother and fetus. Therefore, the researchers wanted to know the levels of HIF-1α in patients with preeclampsia compared with normal pregnancy thus morbidity and mortality of maternal and fetus can be prevented or reduced as expected.

Preeclampsia is a pregnancy-specific syndrome such as reduced organ perfusion due to vasospasm and endothelial activation, which is characterized by increased blood pressure and proteinuria. The onset of hypertension accompanied with proteinuria in gestational age over 20 weeks. Preeclampsia is common in second or third trimester of pregnancy with the highest incidence at 32 weeks of gestational.[6,7]

Previously, the diagnosis of preeclampsia is established based on the presence of the triad of edema, hypertension and proteinuria, but often the triad does not appear and manifest at more severe stages. Nowadays, diagnostic of preeclampsia is to find proteinuria and hypertension. Edema is no longer included because it often appears in normal pregnancy.[8]

Proteinuria occurred due to a defect in the kidney, abnormalities of the endothelium in particular, which is one of the pathogenesis of preeclampsia. As a result, proteinuria that occurred is a long process which has taken place further damage to the glomerulus of kidneys so proteinuria can not be the gold standard for early diagnosis of preeclampsia.[6]

Until now there is no theory about the preeclampsia that considered correct, that is why preeclampsia was called "the disease of theories". Various theories regarding the etiology of preeclampsia should be taken into account in the observation that hypertensive disorders in pregnancy often arise on women whom been exposed to the villi coriallis at the first time, women who were exposed to villikorialis at many times like in the gemelli or hydatidiform mole, women who had a previous vascular disorders and women who are genetically have a predisposition to hypertension in pregnancy.[6,7]

METHODS

The study was conducted at the Obstetrics and Gynecology Department of Prof. Dr. R. D. Kandou General Hospital. This research was carried out from April to June 2014. This study is a cross-sectional analytic approach in preeclampsia and normal pregnancy. Inclusion criteria for mothers who had agreed to participate in the study after receiving an explanation about the research and term that meet the criteria of severe preeclampsia and normal pregnancy. Exclusion criteria are pregnant women with chronic diseases such as diabetes mellitus, kidney disorders, cardiac disorders, chronic hypertension, cancer, multiple pregnancies and intrauterine fetal death.

Cubital venous blood sampling by 5 ml of serum was done and stored in a refrigerator (-20°C), then sent to Jakarta by using ice packs to maintain storage temperatures, the examination of HIF-1α proceed in Prodia Laboratory, Jakarta. The level of HIF-1α serum was done by quantitative ELISA method.

Table 1. Subject Characteristics based on Age, Parity, and Number of Marriages

Characteristics	Group				p
	Normotension		Preeclampsia		
	n	%	n	%	
Age (year)					
< 35	29	76.3	27	71.1	0.602
≥ 35	9	23.7	11	28.9	
Parity					
Primigravida	12	31.6	22	57.9	0.021
Multigravida	26	68.4	16	42.1	
Number of marriages					
1 time	37	97.3	32	84.2	0.047
> 1 time	1	2.7	6	15.8	

RESULTS

This study was conducted on 76 pregnant women who meet the criteria for inclusion in the Polyclinic Obstetrics and Gynecology and maternity room BLU RSUP Prof. Dr. R. D. Kandou, Manado. Thirty eight controls and 38 patients with preeclampsia.

Table 2. The Correlation of Hypoxia Inducible Factor 1 alpha between Preeclampsia, and Normotension Pregnancy

	Mean	SD	p
Normotension	0.092	0.046	0.000
Preeclampsia	0.175	0.212	

DISCUSSION

Basic characteristics of the study sample consisted of several variables including age, parity, number of marriages and the levels of Hypoxia Inducible Factor-1α, 76 pregnant women were divided into 2 groups : group with normotensive pregnancy and preeclampsia group.

Preeclampsia is a symptoms that often occur as a complication of pregnancy and caused by a lot of factors, one of which is the age of the mother during pregnancy is already advanced, it means a higher risk of preeclampsia in pregnant women over the age of 35 years. In a study involving 76 pregnant women, it turns out the largest number in the group under 35 years of age and pregnant with normotensive, while the second highest number in the group under 35 years of age but pregnant with preeclampsia, which found no significant differences between age with preeclampsia. This result contrasts with the results obtained by Duckitt (2005), that the age associated with the incidence of preeclampsia, especially extreme age (> 40 years) had a 2-fold risk of preeclampsia, both primipara and multipara.[8]

Other risk factors that may increase the risk of complications of preeclampsia is primigravida/ first pregnancy. The risk of preeclampsia is generally decreased in the second pregnancy compared to the first pregnancy. Explanation indicates a decreased risk is recurrent maternal exposure and adaptation to specific antigens of the same partner. The difference in risk might explain the gap between births. Have sex with different partner will increase the risk of preeclampsia.[9] In this study, we found a significant positive association between preeclampsia in primigravida than multi gravida. These results are similar to research conducted by Roberts et al (2009) and Nurdi AA (2013), that nulliparity have almost 3-fold risk for preeclampsia. In multipara shows there is a reduced risk that may be caused by maternal exposure to repetitive and adaptation to specific antigens of same couples.[8]

The number of marriages was also said to be one of the risk factors for preeclampsia which in this study, there is a significant correlation between married one time with more than 1 times. This is consistent with research of Skjaerven R (2002) where women who are having sex with different partner will increase the risk of this preeclampsia.[9] This is due to excessive maternal inflammatory response against foreign antigens from different sperm, resulting in a series of events including shallow trophoblast invasion, damage to the formation of spiral arteries, placental infarction and release of pro-inflammatory cytokines that enter the systemic circulation.[10]

Significant relationship between the average levels of HIF-1α in the serum of pregnant women with preeclampsia compared to normotensive pregnancy supports the hypothesis that there is an increment of HIF-1α levels in patients with preeclampsia compared with normotensive pregnancies. There is a lot of evidence to support the occurrence of hypoxia on preeclampsia. Lunell et al., explain that there is a decline of 50% in the utero utero placental circulation in patients with preeclampsia. Caniggia suggested that preeclampsia may occur due to failure increased responsiveness or sensitivity of trophoblast cells to oxygen.[11]

Hypoxia Inducible Factor-1α (HIF-1α) is a key regulator of the cellular response to low oxygen tension and centered on oxygen homeostasis. It is a heterodimer transcription factor composed of two subunits, namely α and β. When HIF-1β is constitutively active, HIF-1α is sensitive to oxygen, are rapidly inactivated and degraded into normoxia state. In a state of low oxygen, HIF is a key regulator of a number of target genes that can induce anaerobic process, reducing the consumption of oxygen or cause angiogenesis to stabilize the vascular environment. HIF can function at all stages of development and placental differentiation. Reshef Tal et al., conducted experiments on mice reported that the increase in HIF-1α can lead to growth retardation (IUGR) and clinical symp-

toms of preeclampsia. This is similar to research conducted by Rajakumar et al., reported that HIF-1α levels did not differ in term pregnancies compared preterm pregnancies without preeclampsia, where as HIF-1α levels increased two-fold in preeclamptic pregnancies compared with normal.[12,13] Stacy Zamudio et al also reported that in the hypoxia state, HIF-1α levels increased by 13 times.[14]

With so much evidence included in this study which found significant differences between the levels of HIF-1α in preeclampsia compared with normotensive so it can be inferred that HIF-1α levels can be used as a predictor of preeclampsia.

CONCLUSION

There is a positive relationship between the levels of HIF-1α in serum of preeclampsia, in which HIF-1α levels in preeclampsia was significantly higher than normotensive pregnancies

REFERENCES

1. Carty DM, Delles C, Dominiczak AF. Preeclampsia and future maternal health. J Hypertens. 2010; 28: 1349-55.
2. Duley L. The global impact of preeclampsia and eclampsia. Semin Perinatol. 2009; 33: 130-7.
3. Badan Penelitian dan Pengembangan Kesehatan Kementerian Kesehatan RI. Riset kesehatan dasar. Jakarta: Kementerian Kesehatan RI; 2013.
4. Maynard SE, Karumanchi SA, Thadhani R. Hypertension and kidney disease in pregnancy. In: Brenner BM, editor. Brenner and Rector's The Kidney. 8th ed. Philadelphia, PA: WB Saunders; 2007.
5. Angsar D. Hipertensi dalam kehamilan. Dalam: Ilmu Kebidanan ed. 4 Jakarta. Yayasan Bina Pustaka Sarwono Prawirohardjo. 2008: 530-67.
6. Cunningham FG, Leveno KJ, Bloom SL et al. Pregnancy hypertension. In: Twickler D, Wendel GD (Eds). Williams Obstetrics 23rd. McGraw Hill Book Company. 2010: 706-56.
7. Sibai B, Dekker G, Kupferminc M. Preeclampsia. Lancet. 2005; 365: 785-99.
8. Duckitt K and Harrington D. Risk factors for preeclampsia at antenatal booking: systematic review of controlled studies. BMJ. 2005; 330(7491): 565-7.
9. Skjaerven R, Wilcox AJ, Lie RT. The Interval Between Pregnancies and The Risk of Preeclampsia. N Engl J Med, 2002; 346 1 (3): 33-8.
10. Matthiesen L, Berg G, Ernerudh J et al. Immunology of Preeclmapsia. Chem Immunol Allergy. 2005; 89: 49-61; Formosa M. The paradox of pregnancy: an update on immunology of early pregnancy. Malta Med J. 2008;20(02): 10-4.
11. Caniggia l, Winter JL. Adriana and Luise Castellucci Award Lecture 2001 Hypoxia Inducible Factor-1. Oxygen Regulation of Trophoblast Differentiation in Normal and Preeclamptic Pregnancies-A Review. Placenta,2002; 16: 47-57.
12. Tal R. The role of hypoxia and hypoxia inducible factor 1 alpha in preeclampsia pathogenesis. Biol Reprod. 2012; 87(6): 134,1-8.
13. Tal R, Shaish A, Barshack I et al. Effects of hypoxia-inducible factor 1 alpha over expression in pregnant mice. Am J Pathology. 2010; 177(6): 2950-62.
14. Zamudia S, Wu Y, Letta F et al. Human placental hypoxia inducible factor 1 alpha expression correlates with clinical outcomes in chronic hypoxia in vivo. Am J Pathol, 2007; 170(6): 2171-9.