

Research Article

The Associated of Serum Inhibin A Levels in Severe Preeclampsia

Hubungan Kadar Inhibin A Serum pada Preeklamsia Berat

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Abstract

Objective: to prove the associated of serum Inhibin A levels in severe preeclampsia.

Methods : This was a cross-sectional study. Subjects consisted of 23 samples of normotensive pregnancy and 23 of samples severe preeclampsia who meet the inclusion and exclusion criteria. This study was conducted and evaluated from September 2016 until December 2016 at the Department of Obstetrics and Gynecology Faculty of Medicine University of Sam Ratulangi Prof. Dr. R. D. Kandou Hospital Manado and satellite hospitals. Samples were analysed using ELISA method at Prodia laboratory. Data were analysed with SPSS version 20.0

Results: Mean serum Inhibin A levels in normotensive pregnancy is 477.22 pg/ml while mean in severe preeclampsia is 2712.39 pg/ml with p-value = 0.000.

Conclusions: Levels of serum Inhibin A in severe preeclampsia significantly higher compared to normotensive pregnancy.

Keywords: inhibin A, normotensive, severe preeclampsia

Abstrak

Tujuan: untuk membuktikan hubungan kadar inhibin A serum pada preeklamsia berat.

Metode: penelitian ini merupakan studi analitik observasional dalam bentuk desain potong lintang. Dilakukan pemeriksaan kadar Inhibin A serum pada 46 sampel ibu hamil yang memenuhi kriteria inklusi dan eksklusi, terdiri atas 23 kelompok preeklamsia berat dan 23 kelompok kehamilan normotesi. Penelitian dilaksanakan dan dievaluasi sejak bulan September 2016 sampai Desember 2016 di Bagian Obstetri dan Ginekologi Fakultas Kedokteran Universitas Sam Ratulangi / RSU Prof. dr. R. D. Kandou Manado dan rumah sakit jejaring. Analisis sampel dilakukan di Laboratorium Prodia Jakartamenggunakan metode ELISA. Data dianalisis dengan SPSS versi 20.0.

Hasil: rerata kadar Inhibin A serum pada kelompok kehamilan normotesi yaitu 477,22 pg/ml sedangkan rerata pada kelompok preeklamsia berat yaitu 2712,39 pg/ml dengan nilai $p=0,000$.

Kesimpulan: kadar Inhibin A serum pada preeklamsia berat lebih tinggi secara bermakna dibandingkan dengan kehamilan normotensi.

Kata kunci: inhibin A, normotensi, preeklamsia berat

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INTRODUCTION

Preeclampsia is an obstetric health problem where the aetiology is unclear and was first diagnosed after 20 weeks of pregnancy. Some experts say that preeclampsia is a syndrome of several causes. Based on the recent classification proposed by the National High Blood Pressure Education Program, the minimum diagnostic criteria for preeclampsia are hypertension, blood pressure $\geq 140/90$ mmHg and proteinuria, urinary protein excretion ≥ 300 mg in 24 hours.^{1,2}

Various biochemical markers based on the pathophysiology of hypertension in pregnancy are proposed with the aim of predicting the progression of pregnancy towards preeclampsia. The latest study, Inhibin A group of glycoproteins produced by placenta syncytiotrophoblast can be used as a predictor of preeclampsia. Several studies have shown that levels of Inhibin A are significantly increased in the circulation of pregnant women with preeclampsia without a clear mechanism. There is even research mentioning Inhibin A increases before preeclampsia occurs.

It is useful for clinical applications in identifying pregnant women at risk for preeclampsia.³⁻⁵ This study aims to prove the association of serum Inhibin A level in severe preeclampsia where this study is expected to provide input in an effort to reduce the incidence of severe preeclampsia.

METHOD

This was a cross-sectional study conducted from September 2016 until December 2016 at Department of Obstetrics and Gynecology Faculty of Medicine Universitas Sam Ratulangi Prof. Dr. R. D. Kandou Hospital Manado and satellite hospitals. The subject of this study consists of 23 samples of normotensive pregnancy and 23 samples of severe preeclampsia who meet the inclusion and exclusion criteria. The inclusion criteria include pregnant women more than 20 weeks gestation, severe preeclampsia, superimposed preeclampsia and eclampsia, and willing to participate in research. Exclusion criteria include pregnant women with chronic

hypertension, heart disease, liver, kidney, and diabetes mellitus. After anamnesis, physical examination and have informed consent, serum samples were taken from as many as 5 cc and put into a sterile sample container, centrifuged and stored at -70°C. Samples were analysed using ELISA method at Prodia laboratory. Data were analysed with SPSS version 20.0. This study has also been approved by the Integrated Health Research Unit (UPKT) Dr Prof. Dr. R. D. Kandou Manado.

RESULT

A total of 23 samples of normotensive pregnancy and 23 samples of severe preeclampsia were recruited for this study.

Table 1 shows the subject of research in the normotensive group of pregnant women. Aged <35 years old group 18 people (78.26%) is the most, high school education group 19 people (82.61%) is found the most in normotensive pregnancy group, which is the most job as pregnancy group, which is the most job as a housemaid 22

Table 1. Subject Characteristics

| Characteristics | Normotensive | Pregnancy | Severe | Preeclampsia |
|------------------------|--------------|-----------|--------|--------------|
| | n | % | n | % |
| Age | | | | |
| < 35 years | 18 | 78.26 | 16 | 69.57 |
| ≥ 35 years | 5 | 21.74 | 7 | 30.43 |
| Education | | | | |
| Bachelor | 3 | 13.04 | 1 | 4.35 |
| Senior High | 19 | 82.61 | 17 | 73.91 |
| Junior High | 1 | 4.35 | 3 | 13.04 |
| Primary | - | - | 2 | 8.69 |
| Job | | | | |
| Civil servant | 2 | 8.69 | - | - |
| Entrepreneur | 2 | 8.69 | 1 | 4.35 |
| Housewife | 19 | 82.61 | 22 | 95.65 |
| Gestational age | | | | |
| 2nd Trimester | - | - | 1 | 4.35 |
| 3rd Trimester | 23 | 100 | 22 | 95.65 |
| Parity | | | | |
| Primigravidity | 6 | 26.09 | 13 | 56.52 |
| Multigravidity | 17 | 73.91 | 10 | 43.48 |

people (95.65%) in severe preeclampsia group, 100% samples were taken at the age of 3rd

trimester pregnancy in normotensive pregnancy, and multigravidity were 17 people (73.91%) in normotensive pregnancy group.

Table 2. Variable Distribution of Age and Blood Pressure (BP) in Normotensive Pregnancy and Severe Preeclampsia

| Clinical Manifestation Variable | Normotensive Pregnancy (Mean ± SD) | Severe Preeclampsia (Mean ± SD) | P-value |
|---------------------------------|------------------------------------|---------------------------------|---------|
| Systolic BP | 113.4 ± 10.632 | 166.96 ± 8.757 | 0.000 |
| Diastolic BP | 72.17 ± 7.952 | 107.83 ± 7.359 | 0.000 |

Table 3. The Association of Serum Inhibin A Levels

| Inhibin A serum Level (pg/ml) | Normotensive Pregnancy | Severe Preeclampsia |
|-------------------------------|------------------------|---------------------|
| Mean | 477.22 | 2712.39 |
| Median | 343.00 | 1448.00 |
| Range | 1236 | 8378 |
| Std. Deviation | 435.92 | 2426.26 |
| 95% Confidence Interval | 288.71 – 665.72 | 1663.20 – 3761.59 |

In Table 3, serum Inhibin A levels in normotensive pregnancy group has mean 477.22, median 343.00, range 1236, std. Deviation 435.92, and 95% Confidence Interval 288.71 - 665.72. While serum Inhibin A levels in severe preeclampsia group has mean 2712,39, median 1448.00, range 8378, std. Deviation 2426.26, and

Table 4. Statistic Test of Serum Inhibin A Levels

| Statistical Test | Value |
|------------------------|---------|
| Mann – Whitney U | 46,000 |
| Wilcoxon W | 322,000 |
| Z | -4,801 |
| Asymp. Sig. (2-tailed) | 0.000 |

95% Confidence Interval 1663.20 - 3761.59

Table 4 shows statistic test of serum InhibinA levels. Mann-Whitney U value is 46,000, and Wilcoxon-W value is 322,000. If converted to a value of Z then the result is -4,801. So in Mann-Whitney test that p = 0,000 can be found which indicated there was a significant difference of serum Inhibin A level between normotensive pregnancy group and severe preeclampsia group (p = 0,000). Finally, it can be concluded that levels of serum Inhibin A in severe preeclampsia significantly higher compared to normotensive pregnancy.

DISCUSSION

Preeclampsia is a syndrome of various causes characterised by an increase in blood pressure with proteinuria in gestational age more than 20 weeks Concentrations of some protein markers in the

maternal circulation increase in preeclampsia. The latest research, Inhibin A is a class of glycoproteins produced by placental syncytiotrophoblast and can be used as a predictor of preeclampsia. The at term placental cells produce Inhibin A, which will increase as a response to inflammatory cytokine in preeclampsia. In preeclampsia, there is a failure of extravillous trophoblast invasion (EVT) in the spiral artery myometrial segment and spiral artery remodelling is ineffective. Placental uterine circulation is maintained with high resistance conditions, resulting in decreased placental perfusion, placental insufficiency and inhibited blood flow to the fetus. Hypoxic placental conditions increase the production and synthesis of reactive oxygen species (ROS). ROS is involved in the stimulation of α and β A Inhibin gene expression by the placenta, resulting in elevated serum Inhibin A levels. In addition to increased ROS, placental hypoxia leads to increased production of cytokines, such as IL-1 β and TNF- α . IL-1 β increases production and synthesis of Inhibin A, while TNF- α inhibits synthesis of InhibinA.⁶⁻⁹

The subject of this study consists of 23 samples normotensive pregnancy and 23 samples severe preeclampsia, using age, education, marriage, and maternal parity as subject characteristics.

Based on the subject characteristics, the highest number of maternal age in normotensive pregnancy group and severe preeclampsia group was <35 years, wherein the group of normotensive pregnancy are 18 people (78.26%), and severe

preeclampsia group are 16 (69.57%). For high school education group, the highest number is in normotensive pregnancy which has 19 people (82.61%), and severe preeclampsia group which has 17 people (73.91%). Housemaid job is the highest in normotensive pregnancy group, which has 19 people (82.61%) and severe preeclampsia group which has 22 people (95.65). 100% of the samples were taken at the age of 3rd trimester of pregnancy in normotensive pregnancy. The last subject characteristics were parity, wherein the group of normotensive pregnancy, the highest number was found in multigravida which has 17 people (73.91%) whereas in the group of preeclampsia the highest was primigravida which has 13 people (56.52%). This is consistent with the theory that the frequency of preeclampsia is higher in primigravida than multigravida because of the insufficient formation of antibody inhibitors that increases the risk of preeclampsia.^{10,11}

Inhibin A serum test in this study showed significantly different results in the group of normotensive pregnancy and severe preeclampsia group. The mean value of Inhibin A serum level in the severe preeclampsia group was higher than the normal group, which is 477.22 pg/ml in the normotensive pregnancy group and 2712.39 pg/ml in the severe preeclampsia group. From the statistic test of serum Inhibin A level, $p = 0.000$ was obtained, meaning that there was a significant difference of serum Inhibin A level in normotensive pregnancy group and severe preeclampsia group. This proves there is a correlation of serum Inhibin A level with severe preeclampsia events.¹⁰

The results of this study support the researches that have been done by previous researchers. Initial studies about increased Inhibin A in severe preeclampsia were first performed by Muttukhrisna (1997) with a significant increase in Inhibin A serum on preeclampsia. The study was conducted on 20 women with normal pregnancies and 20 women with preeclampsia. He concluded that in normal pregnancy, Inhibin A levels will increase in the third trimester, and show a tenfold increase level in pregnant women with severe preeclampsia. Whereas in the second trimester, Inhibin A levels showed an increase in both maternal blood serum and in amniotic fluid of pregnant women which progressed toward preeclampsia and that elevated level is related to

the severity of preeclampsia symptoms. Increased Inhibin A level in preeclampsia is due to the production of placental tissue and illustrate that preeclampsia occurs in abnormal placentas and as a result of failed trophoblast function.^{4,5}

Another study on Inhibin A serum level in severe preeclampsia was performed by Zeeman et al. (2005). The study was conducted on 232 pregnant women who observed for two months. Inhibin A serum level showed an increase in mild preeclampsia and severe preeclampsia, whereas in chronic hypertension and hypertension in pregnancy have an Inhibin A level almost equal to normal pregnancy.^{12,13}

El-Gharib and Morad (2010) said that Inhibin A serum level in maternal could predict preeclampsia. The study was conducted on 326 primigravida who performed prenatal care at Tanta University Hospital, Egypt. Pregnancy is confirmed by ultrasound, and informed consent is required on all expectant mothers. Women with multifetal pregnancies, infections, diabetes mellitus, and a history of hypertension or kidney disease were excluded from the study. And the subjects of the study were divided into 2 groups. The results showed that Inhibin A serum level had a very high increase in severe preeclampsia.¹⁴

CONCLUSION

Levels of serum Inhibin A in severe preeclampsia significantly higher compared to normotensive pregnancy. So it can be concluded that serum Inhibin A level is associated with severe preeclampsia.

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