Vol. 1, No. 1, Jan-Jun 2017

ANDALAS OBSTETRICS AND GYNECOLOGY JOURNAL

Alamat Korespondensi:
Ruang Redaksi Andalas Obstetrics and Gynecology Journal, Lantai 3 PPDS Obstetri dan Ginekologi Universitas Andalas, RSUP DR. M. Djamil Padang, Jl. Perintis Kemerdekaan Padang, Sumatera Barat 25127

Website:
http://jurnalobgin.fk.unand.ac.id/index.php/JOE

eISSN : 2579-8324 pISSN : 2579-8323

RESEARCH

Difference in Mean Maternal Activin A Serum Levels on Severe Preeclampsia and not Severe Preeclampsia

Dovy Djanas[1], Bayu Pramudyo Ariwibowo[2], Hafni Bachtiar[3]

Affiliations *: 1. Sub Division of Maternal Fetal Medicine, Obstetrics and Gynecology Department, Faculty of Medicine, Andalas University, Dr. M. Djamil Central General Hospital Padang; 2. Resident of Obstetrics and Gynecology, Faculty of Medicine, Andalas University, Dr. M. Djamil Central General Hospital Padang; 3. Public Health Department, Faculty of Medicine, Andalas University Padang*

Correspondence: *Dovy Djanas, email: dovy.djanas@yahoo.com, Hp: 081266194050*

Abstract

At the start of preelampsia there is a failure of cytotrophoblst invasion into the maternal spiral arteries that will lead to decreased uteroplacetal perfusion which will be followed by the failure of the unit fetoplacenter to get enough oxygen from the room intervillous that ultimately lead to a state of hypoxia in placenta. This will cause the expenditure of TNF-α dan IL-1β from placenta and a factors called hypoxia-inducible transcription factors that will spur the trophoblast to produce activin A lot more. This research was conducted by cross sectional method in maternal room of obstetrics and gynecology department of Central General Hospital of Dr. M. Djamil Padang from August 2015 until February 2016 with 20 patients of severe preeclampsia and 20 patients not severe preeclampsia, who met inclusion criteria and there is no exclusion criteria. Then performed statistical analysis using Mann-Whitney test to determine difference in mean maternal activin A serum levels of severe preeclampsia and not severe preeclampsia. The mean maternal serum levels of activin A in severe preeclampsia is 32,55 ± 1,84 ng/ml and in pregnancy with no severe preeclampsia is 8,59 ± 0,59 ng/ ml. Difference in mean maternal serum level of activin A in the two groups was statistically significant (p=0,001). Maternal serum activin A levels is significantly higher in severe preeclampsia than pregnancy with no severe preeclampsia.

Keywords: *Activin A, severe preeclampsia, not severe preeclampsia*

INTRODUCTION

Preeclampsia is a disease syndrome that can cause interference with various organs. Until now, preeclampsia is still a major complication in pregnancy and a major cause of death and morbidity both maternal and perinatal.[1] The incidence of preeclampsia is different for each country. The incidence ranges from 4 - 9% in pregnant women, 3 - 7% in nulliparous, and 0.8 - 5% in multiparous. The incidence of preeclampsia in several hospitals in Indonesia is still quite high. Data from the medical records of patients treated at the Obstetrics and Gynecology Department of Dr. M. Djamil Padang in 2010, there were 113 cases of severe preeclampsia from 1295 deliveries (8.7%), in 2011 around 119 cases out of 1287 deliveries (9.2%) and in 2012 about 140 cases out of 1301 deliveries (10,76 %).[2] Data from the medical records of patients treated at the Obstetrics and Gynecology Department, Dr. M. Djamil Padang in 2013 found 338 cases of preeclampsia and eclampsia, 259 cases of severe

Received 8 December 2016
Accepted 30 December 2016
Correspondence: Dovy Djanas, email: dovy.djanas@yahoo.com

Vol. 1, No. 1, Jan-Jun 2017
ANDALAS OBSTETRICS AND GYNECOLOGY JOURNAL
Alamat Korespondensi:
Ruang Redaksi Andalas Obstetrics and Gynecology Journal, Lantai 3 PPDS Obstetri dan Ginekologi Universitas Andalas, RSUP DR. M. Djamil Padang, Jl. Perintis Kemerdekaan Padang, Sumatera Barat 25127
eISSN : 2579-8324 pISSN : 2579-8323
Website:
http://jurnalobgin.fk.unand.ac.id/index.php/JOE

preeclampsia, 79 cases of eclampsia, 6 deaths due to preeclampsia, and 8 deaths due to eclampsia.

Early preeclampsia occurs. Many placental factors are seen in the maternal circulation during normal pregnancy, increasing in severe preeclampsia. These include several inflammatory cytokines, corticotropin-releasing hormone, free radicals, and activin A. All can stimulate the maternal inflammatory response. Excessive release of this factor could be due either to oxidative stress resulting from the intermittent placental blood supply, as seen in the placenta from some cases of preeclampsia or perhaps the product of greater placental mass such as multiple pregnancies.

Failure of invasion of the cytotrophoblast into the maternal spiral artery. This will lead to a decrease in uteroplacental perfusion which will be followed by failure of the fetoplacental unit to get sufficient oxygen from the intervillous space which ultimately leads to a hypoxic state in the placenta. This will cause the removal of TNF-α and IL-1β from the placenta as well as a factor called hypoxia-inducible transcription factors which will stimulate trophoblasts to produce more activin A.[5] This is needed to stimulate more villus cytotrophoblast cells to migrate to extravillous cytotrophoblasts and will become invasive cytotrophoblasts that will invade the vascular endothelium deeper in the spiral arteries. All of this is a process of the placenta to ensure adequate oxygen supply for fetal development during pregnancy.

In this process, there is an increase in the secretion of substances secreted by trophoblast cells such as TNF-α and IL-1β cytokines and lipid peroxidases where TNF-α and IL-1β will activate vascular endothelial cells and monocytes and macrophages in the peripheral blood circulation to secrete activin. A. While lipid peroxidase will cause wider vascular endothelial dysfunction. This will lead to increased levels of activin A in the maternal blood circulation at the onset of preeclampsia. Increased levels of activin A occur early in pregnancy before the clinical manifestations of preeclampsia appear so that increased levels of activin A can be used to predict the onset of preeclampsia at the next gestational age.

Apart from preeclampsia, elevated levels of activin A were also found in conditions of systemic inflammation, chronic hypertension, diabetes mellitus, multiple pregnancy, and premature labor. In conditions of systemic inflammation, diabetes mellitus and premature delivery of cytokines TNF-α and IL-1β play an important role in increasing levels of activin A. Meanwhile, in multiple pregnancies, placental factors, and trophoblast dysfunction are factors that cause the increase in levels of activin A.[6]

Activin is a glycoprotein belonging to the Transforming Growth Factor-β superfamily, a group of proteins that control the proliferation and differentiation of cells from many-body systems. Activin is composed of β subunits, both homodimers and heterodimers and consists of activin A (βA-βA), activin B (βB -βB) or activin AB (βA-βB). body. Initially, activin was thought to be a member of the hypothalamic-pituitary-gonadal axis and was called activin because it inhibits inhibin and stimulates the action of the pituitary in producing FSH. Recently the

Received 8 December 2016
Accepted 30 December 2016
Correspondence: Dovy Djanas, email: dovy.djanas@yahoo.com

Vol. 1, No. 1, Jan-Jun 2017
ANDALAS OBSTETRICS AND GYNECOLOGY JOURNAL
Alamat Korespondensi:
Ruang Redaksi Andalas Obstetrics and Gynecology Journal, Lantai 3 PPDS Obstetri dan Ginekologi Universitas Andalas, RSUP DR. M. Djamil Padang, Jl. Perintis Kemerdekaan Padang, Sumatera Barat 25127
eISSN : 2579-8324 pISSN : 2579-8323
Website:
http://jurnalobgin.fk.unand.ac.id/index.php/JOE

expression of activin mRNA subunits is found in various organs other than the gonads, namely the brain, pituitary, thyroid, adrenal cortex, pancreas, bone marrow, and reproductive organs.[7] In pregnant women, activin is mostly produced by the placenta, decidual cells, and membranes. fetus. [7]

In a normal pregnancy, the cytotrophoblast cells induced by activin A successfully invade the vascular endothelium of the spiral arteries to the tunica media and convert them into an elastic channel that allows the adequate blood supply to the developing fetus. This will ensure adequate uteroplacental oxygenation for fetal development during pregnancy. [6]

Preeclampsia begins with the failure of cytotrophoblast cell invasion in the spiral arteries, which prevents the conversion of the spiral arteries into a channel that has low resistance. As a result, there is a decrease in uteroplacental perfusion and followed by failure of the fetoplacental unit to get sufficient oxygen from the intervillous space which ultimately leads to a hypoxic state in the placenta. This will cause the release of TNF-α and IL -1β from the placenta as well as a factor called hypoxia-inducible transcription factors which will stimulate trophoblasts to produce more activin A. [8] This is necessary to stimulate more villus cytotrophoblast cells to migrate to extravillous cytotrophoblasts and eventually become invasive cytotrophoblasts which will invade the vascular endothelium deeper in the spiral arteries. It is a process of the placenta to ensure an adequate supply of oxygen for fetal development during pregnancy. This will all cause an increase in the level of activin A in the maternal blood circulation. [5]

In addition to increasing the production of activin A in the placenta by inducing trophoblast cells, it turns out that TNF-α and IL-1β will also stimulate monocytes and macrophages in the peripheral blood circulation to produce activin A where the levels of activin A produced by monocytes and macrophages will increase accordingly. with increased levels of cytokines TNF-α and IL-1β. TNF-α and IL-1β will also activate vascular endothelial cells to produce activin A. This will all cause the activin A levels to rise prematurely before the clinical manifestations of preeclampsia appear.

METHOD

This study was conducted using a cross-sectional study method to determine the difference in mean maternal serum activin A levels between severe preeclampsia and non-severe preeclampsia at RSUP Dr. M Djamil Padang. The study was started in August 2015 to February 2016. The population of this study was all single pregnant women with a gestational age of more than 20 weeks who were diagnosed with severe preeclampsia, and as controls for normotensive pregnant women who were treated at the Obstetrics and Gynecology Department of Dr. M General Hospital. Djamil Padang. In this study, the sample was divided into 2 groups, namely the pregnant group with PEB of 20 people and the pregnant group with 20 people without severe preeclampsia. All patients who met the inclusion criteria were

Received 8 December 2016
Accepted 30 December 2016
Correspondence: Dovy Djanas, email: dovy.djanas@yahoo.com

Vol. 1, No. 1, Jan-Jun 2017
ANDALAS OBSTETRICS AND GYNECOLOGY JOURNAL
Alamat Korespondensi:
Ruang Redaksi Andalas Obstetrics and Gynecology Journal, Lantai 3 PPDS Obstetri dan Ginekologi Universitas Andalas, RSUP DR. M. Djamil Padang, Jl. Perintis Kemerdekaan Padang, Sumatera Barat 25127
eISSN : 2579-8324 pISSN : 2579-8323
Website:
http://jurnalobgin.fk.unand.ac.id/index.php/JOE

briefed on the study to be carried out. Patients who are willing to take part in the research fill out the consent form that has been provided (consent form attached).

Anamnesis is carried out by noting: name, age, medical registration number, clear address, contact phone number, parity, the first day of last menstruation (HPHT) and determine gestational age, for patients whose last menstrual period is unclear, gestational age is determined based on the early ultrasound on current pregnancy by both the researcher and Chief Resident Obgyn.

Physical examination was performed: blood pressure, pulse rate, breath, temperature, urine protein, and patellar reflex. If the diagnosis is severe preeclampsia, apply the initial SM regimen, and continue examining the obstetric status.

Examination of blood sugar while using a glucometer. Insert an awl (lancet) in the tool (lancet device). Clean the fingertips with an alcohol swab. Pierce the fingertips, wipe the first blood out with a cotton swab, and let a small circle of blood form on the fingertip. Attach the end of the test strip to the circle of blood until evenly wet. View the results on the glucometer.

A total of 5 cc of blood was inserted into a plain tube, used to check the serum activin A levels. Blood samples were checked by calculating the serum levels of activin A using the Active free Activin A kit from DSL (Diagnostic Systems Laboratories) and using the ELISA technique (Enzyme-Linked Immunosorbent Assay) in ng / mL units. If the blood sample is not checked immediately, it can be stored in a refrigerator with a temperature of 2 - 8 0C for 24 hours or stored at -20 0C for 30 days. The examination was carried out at the Prodia Padang Laboratory. In this study, the analysis was carried out using the Statistical Package for the Social Science (SPSS) program version 15.

RESULTS

Research Sample Characteristics

Of the 40 samples that met the inclusion and exclusion criteria, it was found that the characteristics of the study sample were based on age, parity, and GDS as shown in Table 1.

Table 1. Characteristics of the Research Sample

Variable	Preeclampsia n=20		Not preeclampsia n=20		p
	Mean (SD)	n (%)	Mean (SD)	n(%)	
Maternal age (year)	32.45(6.10)		32.05(5.11)		0.67
Blood sugar	107.15(13.65)		101.20(15.97)		0.21
Gravida					
- Primigravida		5 (25)		5(25)	1.00
- Multigravida		15 (75)		15 (75)	

Based on the characteristics of the age of the respondents in table 4.1, it was found that the mean age of the group with severe preeclampsia was higher than the mean value in the non-severe preeclampsia group (32.45 ± 6.10: 32.05 ± 5.11). Statistically, this difference was

Received 8 December 2016
Accepted 30 December 2016
Correspondence: Dovy Djanas, email: dovy.djanas@yahoo.com

Vol. 1, No. 1, Jan-Jun 2017
ANDALAS OBSTETRICS AND GYNECOLOGY JOURNAL
Alamat Korespondensi:
Ruang Redaksi Andalas Obstetrics and Gynecology Journal, Lantai 3 PPDS Obstetri dan Ginekologi Universitas Andalas, RSUP DR. M. Djamil Padang, Jl. Perintis Kemerdekaan Padang, Sumatera Barat 25127
eISSN : 2579-8324 pISSN : 2579-8323
Website:
http://jurnalobgin.fk.unand.ac.id/index.php/JOE

not significant, as seen from the p-value of 0.67. This shows that the age in patients with severe preeclampsia is equivalent to non-severe preeclampsia.

In the preeclampsia and non-severe preeclampsia study subjects, there were more multigravida pregnant women than primigravidas, namely 15 (75%) multigravidas compared to 5 (25%) primigravidas. This difference was not significant (p = 1.00). In this study, the mean level of GDS in the preeclampsia group was 107.15 mg/dl and in the non-severe preeclampsia group was 101.20 mg/dl. Statistically, this difference was not significant, seen from the p-value of 0.21.

Differences in mean serum activin A levels between groups of severe preeclampsia and non-severe preeclampsia.

The average level of activin A in the preeclampsia group was 32.55 ng / mL, while the non-severe preeclampsia group had an average activin A level of 8.59 ng / mL. This difference is statistically significant with a p-value of 0.001.

Table 2. Differences in maternal serum activin A levels between non-severe preeclampsia and severe preeclampsia.

	Not Severe Preeclampsia n = 20	Severe Preeclampsia n = 20	*p*
Mean (SD)	8,59(0,59)	32,55(1,84)	0,001

DISCUSSION

Characteristics

A study was carried out on 40 pregnant women with a mean gestational age of 37 ± 1.60 weeks who were tested for activin A. The extreme age of pregnant women (too young or too old) is one of the risk factors for preeclampsia. In this study, there was no difference in the mean age of pregnant women between the preeclampsia and non-preeclampsia groups. Clinically, the mean age of subjects in the preeclampsia group was 32.45 ± 6.10 and neither preeclampsia nor 32.05 ± 5.11 were included in the extreme age for pregnancy.

Research conducted by Uzma Shamsi et al in Pakistan on risk factors for the incidence of preeclampsia found that the incidence of preeclampsia was found mostly at the age of 19-34 years.[10] According to Cunningham FG et al, the incidence of preeclampsia increases in women over 35 years of age.

In this study, there was no significant difference in the age of pregnant women who experienced preeclampsia and normal pregnancy with a p-value of 0.67. This study is following a study conducted by Jeffrey A Keelan et al in Auckland, New Zealand which states that there is no significant difference between the age of pregnant women who experience preeclampsia compared to normal pregnancies.11 Muttkrishna et al conducted a cross-

Received 8 December 2016
Accepted 30 December 2016
Correspondence: Dovy Djanas, email: dovy.djanas@yahoo.com

Vol. 1, No. 1, Jan-Jun 2017
ANDALAS OBSTETRICS AND GYNECOLOGY JOURNAL
Alamat Korespondensi:
Ruang Redaksi Andalas Obstetrics and Gynecology Journal, Lantai 3 PPDS Obstetri dan Ginekologi Universitas Andalas, RSUP DR. M. Djamil Padang, Jl. Perintis Kemerdekaan Padang, Sumatera Barat 25127
eISSN : 2579-8324 pISSN : 2579-8323
Website:
http://jurnalobgin.fk.unand.ac.id/index.php/JOE

sectional study on 310 pregnant women in America in 2000 and it was found that there was no significant difference in the age of pregnant women between the preeclampsia group and the control group.[8]

Diabetes mellitus is one of the confounding factors that can influence the level of activin A through the mechanism of vascular endothelial dysfunction and the release of TNF-α and IL-6 cytokines. In this study, blood sugar checks were carried out to screen for diabetes mellitus. The results of mean blood sugar at the same time were obtained in the preeclampsia group compared to the non-preeclampsia group. Clinically the results of blood sugar while in these two groups were still within normal limits. This is consistent with a study conducted by Gallinelli in Rome that showed that activin A levels were higher in people with gestational diabetes than controls at the same gestational age.[12]

Cunningham FG et al stated that the risk of severe preeclampsia was increased in nulliparous compared to multiparous.1 The study found parity of patients in the same study subjects between the preeclampsia and non-preeclampsia groups. The results of further statistical analysis, the difference in parity between the two groups did not have a significant difference with a p-value of 1.00. This is following a cross-sectional study conducted by Ling Yu et al in China which stated that there was no significant difference in parity between the severe preeclampsia and non-preeclampsia groups.[5]

Activin A levels

Preeclampsia begins with the failure of the cytotrophoblast invasion of the spiral arteries, which prevents the conversion of the spiral arteries to a channel that has low resistance. As a result, there is a decrease in uteroplacental perfusion and followed by failure of the fetoplacental unit to get sufficient oxygen from the intervillous space which ultimately leads to a hypoxic state in the placenta. This results in the removal of TNFα and IL-ß from the placenta as well as a factor called hypoxia-inducible transcription factors. This hypoxic condition causes hyperplasia of trophoblast cells resulting in more activin-A.[13]

In this study, it was found that the mean level of activin A in the serum of the two groups was different, where the mean level of activin A in the preeclampsia group was higher (32.55 ng / mL) compared to the non-severe preeclampsia group (8.59 ng / mL). Patients with preeclampsia will begin to get an increase in the level of activin A at 15-19 weeks of pregnancy, where a significant increase in levels is found at 21-25 weeks of gestation compared to pregnancies without severe preeclampsia.5 Maternal serum activin A levels will continue to increase until term pregnancy. A cross-sectional study conducted by Ling Yu et al in China from November 2005 to November 2007 on 95 people in the Han population showed that activin A levels were higher in the preeclampsia group compared to controls from 25 weeks of gestation to term. Activin A levels increased 3.6 times, 4.2 times and 3.5 times compared to controls at 25-30 weeks of gestation, 31-35 weeks, and 36-40 weeks,

Received 8 December 2016
Accepted 30 December 2016
Correspondence: Dovy Djanas, email: dovy.djanas@yahoo.com

Vol. 1, No. 1, Jan-Jun 2017
ANDALAS OBSTETRICS AND GYNECOLOGY JOURNAL
Alamat Korespondensi:
Ruang Redaksi Andalas Obstetrics and Gynecology Journal, Lantai 3 PPDS Obstetri dan Ginekologi Universitas Andalas, RSUP DR. M. Djamil Padang, Jl. Perintis Kemerdekaan Padang, Sumatera Barat 25127
eISSN : 2579-8324 pISSN : 2579-8323
Website:
http://jurnalobgin.fk.unand.ac.id/index.php/JOE

respectively. The level of activin A which increases in early pregnancy both in pregnancies with and without severe preeclampsia means that activin A can be used to predict the incidence of preeclampsia at the next gestational age.[5]

Activin A at a level of 1-10 ng / mL stimulates the production of MMP2 and pro-MMP 9 so that villus cytotrophoblasts migrate into extravillous cytotrophoblasts and cause cytotrophoblasts to become more invasive. All of this is necessary for the successful invasion of cytotrophoblast cells into the vascular endothelium to allow the conversion of the spiral arteries to become elastic and has low resistance lumen which is necessary to maintain normal pregnancy continuity. Higher levels of activin A (25- 100 ng / mL) fail to induce MMP production and increase the apoptosis of trophoblast cells.[5]

After carrying out the Mann-Whitney test - test on a sample of the severe preeclampsia group compared to the group without severe preeclampsia showed that there was a significant difference in the mean serum level of activin A in the severe preeclampsia group (32.55 ± 1.84 ng / mL) compared to the pregnancy group. without preeclampsia (8.59 ± 0.59 ng / mL) with a p-value of 0.00. This is consistent with a study conducted by S Muttkrishna et al in America in 2006. Muttukrishna et al. Conducted a retrospective cross-sectional study of 40 pregnant women who performed antenatal care and found that serum maternal activin was higher in the preeclampsia group compared to controls with a p-value of 0.001.[8]

The strength of this study is the finding of a significant difference between the serum levels of maternal activin A in severe preeclampsia and normal pregnancies. The weakness of this study is that not all samples are subjected to a complete investigation to rule out other confounding factors. To rule out confounding factors, only routine laboratory examinations and anamnesis of the history of the disease are performed.

CONCLUSION

The mean serum level of maternal activin A in patients with severe preeclampsia was 32.55 ± 1.84 ng / mL. The mean serum level of activin A in normal pregnancy was 8.59 ± 0.59 ng / mL. There is a significant difference in the mean serum level of activin A in severe preeclampsia and normal pregnancy.

REFERENCES

1. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Gilstrap L, and Wenstrom KD. Williams Obstetrics (24th Edition ed.). The McGraw-Hill Companies. New York. 2014.
2. Zilfira D. Adiponektin pada Preeklamsia. Bagian Obstetri dan Ginekologi FK Unand/ RS Dr. M. Djamil Padang. Padang. 2012.
3. Lubis DN. Gambaran Kematian Ibu di Bagian Obstetri Ginekologi RSUP Dr. M. Djamil Padang Tahun 2011-2012. Bagian Obstetri dan Ginekologi FK UNAND. Padang. 2013.

Received 8 December 2016
Accepted 30 December 2016
Correspondence: Dovy Djanas, email: dovy.djanas@yahoo.com

Vol. 1, No. 1, Jan-Jun 2017
ANDALAS OBSTETRICS AND GYNECOLOGY JOURNAL
Alamat Korespondensi:
Ruang Redaksi Andalas Obstetrics and Gynecology Journal, Lantai 3 PPDS Obstetri dan Ginekologi Universitas Andalas, RSUP DR. M. Djamil Padang, Jl. Perintis Kemerdekaan Padang, Sumatera Barat 25127
eISSN : 2579-8324 pISSN : 2579-8323
Website:
http://jurnalobgin.fk.unand.ac.id/index.php/JOE

4. Redman. Pregnancy-related hypertension. Dalam: Maternal-Fetal Medicine Principles and Practice. Edisi 5. Saunders. Philadelpia: 2012. 859-892.
5. Ling Yu, Li Dong, Liao Q P, high levels of activin A detected in preeclamptic placenta induce trophoblast cell apoptosus by promoting nodal signaling. J Clin Endocrinol Metab 2012. 97(8): E1370-E1379.
6. Silver HM, et al. Mechanism of increased maternal serum total activin A and inhibin A in preeclampsia. J Soc Gynecol Investig. 2008. 9: 308-12
7. Stefano L, Florio P, Reis FM, Petraglia F. Expression and secretion of activin A: possible physiological and clinical implication. Euro J Endocrinol. 2001. 225- 36.
8. Muttukrishna S, Groome N, Redman, Sargent. Serum inhibin A and activin A are elevated prior to the onset of preeclampsia. Hum Reprod. 2006. 15:1640-5.
9. Davidson E, Riley S, Robert S, Shearing C, Groome N. Maternal serum activin, inhibin, human chorionic gonadotropin and α-fetoprotein as second trimester predictors of preeclampsia. BJOG. 2005. 110: 46-52.
10. Wallace E, Kolsky M, Edwards, Baker, Jenkin G. Maternal serum activin A levels in association with intrauterine fetal growth restriction. BJOG. 2009. 110:306-10.
11. Jeffrey A, Tailor R, Schellenberg JC. Serum activin A, inhibin A, and follistatin concentrations in preeclampsia or small for gestational age pregnancies. Elsevier. 2002. 99: 267-74.
12. Gallinelli, Gennazeni AD, Matteo ML, Caruso A, Woodruff. Episodeic secretion of activin A in pregnant women. Euro J Endocrinol. 1996. 135:340-4.
13. Keelan JA, Tailor R, Schellenberg J, Groome N, Mitchel M, and North R. Serum Activin A, Inhibin A and Follistatin Concentrations in Preeclampsia or Small for Gestational Age Pregnancies. Am J Obstet Gynecol. 2007. 99: 267-74.

Received 8 December 2016
Accepted 30 December 2016
Correspondence: Dovy Djanas, email: dovy.djanas@yahoo.com