Original Article

Higher placental activin-A (ACV-A) and inhibin-A (INH-A) in preeclampsia placenta mother compare to diabetic mother

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ABSTRACT

Preeclampsia (PE) is a systemic disorder that appears during pregnancy and results in complications in more than 3-6% of deliveries in developed countries. This disease is also the largest leading cause of maternal mortality in many countries, especially in developing countries such as Indonesia. Hence, early diagnosis of preeclampsia is important in young pregnancy to decrease mortality. Recently, activin A and inhibin A were proposed as new candidates for biomarkers in early diabetes in pregnancy. However, there is no information regarding its value in pre-eclampsia and diabetic pregnancy. Herein we conduct a study to determine the value of activin-A and inhibin-A between of preeclampsia mother and a diabetes mellitus mother. Placental samples were collected from 87 mothers undergoing cesarian delivery, which were 29 samples from healthy mothers, 29 samples from diabetic mothers, and 29 samples from preeclampsia mothers. Placentas were obtained after the mother agreed to informed consent from 3 private hospitals in Surabaya. After undergoing processing and homogenizing, placenta tissue was measured for its activin-A and inhibin-A using the ELISA method. Activin-A level placental from the healthy mother group was 0.62 mIU / ml, diabetic mother group was 1.05 mIU / ml, and preeclampsia mother group was 1.23 mIU / ml. The average level of inhibin-A in healthy mothers was 0.45 mIU / ml, diabetes mother group was 0.97 mIU / ml, and preeclampsia mother group was 1.10 mIU / ml. The conclusion is that placental activin-A and inhibin-A levels both in preeclampsia pregnancy have higher values than in diabetes mothers.

Keywords: Activin-A, Diabetes mellitus, Inhibin-A, Preeclampsia

Introduction

Preeclampsia is a serious health disorder that occurs during pregnancy and can cause problems in more than 3-6% of deliveries in developed countries. In addition, preeclampsia is also a major cause of maternal death, especially in developing countries such as Indonesia [1]. Preeclampsia can be defined as a condition in which the blood pressure of pregnant women rises significantly, reaching 140 mmHg for systolic pressure and 90 mmHg for diastolic pressure, especially in pregnancy after 20 weeks. Preeclampsia can become more serious with additional symptoms, which include an increase in blood pressure that exceeds the normal threshold of more than 160 mmHg (systolic pressure) and 110 mmHg (diastolic pressure). In addition, liver dysfunction can be detected from an increase in SGOT and SGPT enzymes in blood tests, as well as an increase in serum creatinine levels exceeding 1.1 mg / dL, or a doubling increase in urea from values considered normal, especially in patients who have not previously had kidney problems. Other symptoms include visual impairment and complaints of headaches [2].

The prevalence of preeclampsia varies, ranging from 5-15% of all pregnancies. In developing countries, the incidence tends to range between 3-10% for preeclampsia and 0.3-0.7% for eclampsia. In Europe and the United States, the incidence of preeclampsia is usually around 5%, while eclampsia occurs in the range of 0.05-0.1%. At Dr. Soetomo Hospital in 2000, it was documented that there were 10.68% cases of preeclampsia. This

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syndrome becomes one of the main causes of serious complications for both pregnant women and newborns, causing the mortality rate of pregnant women to reach around 18%, which is the second highest in the world [3]. At Dr. Soetomo Hospital, this disease even became the leading cause of death in 2001, with an incidence of around 48.27% [4].

Tissues contained in the uterus, including the placenta, amnion, chorion, and decidua, have an important role in secreting hormones and cytokines that regulate physiological interactions between mother and fetus. They also play an important role in programming the mother's endocrine system as well as sending signals that regulate the labor process. Changes in this hormone vary between normal pregnancy and pathological pregnancy and can be used as an indicator for the diagnosis or prediction of diseases that may occur during pregnancy. Recent studies have revealed the huge role of placental hormones in detecting pregnancy diseases. Recent research has shown that several placental hormones can be detected in maternal circulation, fetal circulation, and amniotic fluid. Elevated levels of these placental hormones in maternal blood, fetal umbilical cord, and amniotic fluid clinically indicate increased production of placental hormones in response to adaptation to potentially adverse environmental conditions, such as hypertension, hypoxia, infection, or abnormalities in the fetus and placenta [5].

A number of biochemical indicators are based on the pathophysiology of hypertension during pregnancy, intended to predict the development of preeclampsia. Recent findings, namely activin-A, and inhibin-A, which belong to the group of glycoproteins produced by placental syncytiotrophoblasts, have potential as predictive factors for preeclampsia. Activin and inhibin are part of the TGF-β family which includes 33 members, originally known as regulators of follicle-stimulating hormone (FSH) and red blood cell production (erythropoiesis). However, activin and inhibin have been involved in diverse biological processes, from the early stages of embryonic development to the performance of highly specialized functions in fully differentiated cells and tissues [5, 6].

Materials and Methods

This research was conducted at the Physiology Laboratory of the Faculty of Medicine, Universitas Brawijaya, Malang. Ethical Clearance was issued by the Ethical Comittee of Faculty Medicine Wijaya Kusuma University of Surabaya no 8/SLF/FK/UWKS/2023.

Placentas were obtained from patients in 3 private hospitals in Surabaya, who were willing to be research subjects and met the inclusion criteria. There were 87 samples, including 29 samples in normal conditions, 29 samples in diabetic conditions, and 29 samples in preeclampsia conditions. Activin-A and INH-A levels are serum glycoprotein levels produced by syncytiotrophoblasts, whose level measurements are carried out by the ECLIA method and the results are expressed in mIU/L units.

Results and Discussion

The results of the study obtained the average measurement of normal pregnancy, diabetes mellitus, and preeclampsia, the results of the study are presented in **Figure 1** below.

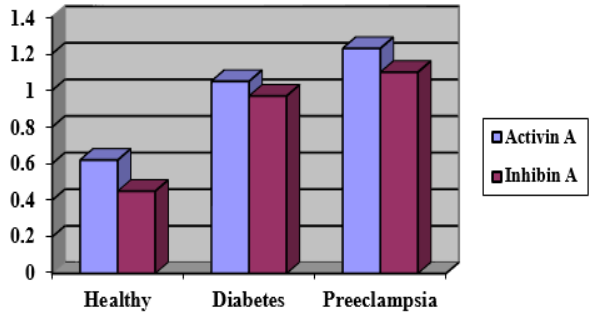

Figure 1. Placental Activin-A and Inhibin-A in Healthy Mother, Diabetes and Preeclampsia in mIU/ml

Where normal pregnancy shows that the average level of activin-A is 1.23 mIU / ml, in pregnancy in diabetic conditions has an average of 1.05 mIU / ml average in pregnancy in preeclampsia conditions of 0.62 mIU / ml. Another case with the average levels of inhibin-A is in normal pregnancy at 1.10 mIU / ml, pregnancy in diabetes conditions at 0.97 mIU / ml, and pregnancy in preeclampsia conditions at 0.45 mIU / ml. In a normal pregnancy, Inhibin A is produced by granulosa cells, and the main role of Inhibin A is in preparing the endometrium for implantation and in the process of decidualization of the endometrial stroma. When trophoblasts begin to invade decidua, the role of Inhibin A, Activin, and various other growth hormones in normal pregnancy can usually be detected around day 7 to 8 of gestation. It is important to note that Activin and Inhibin A have conflicting roles, where Activin supports the process of trophoblastic invasion, while Inhibin A and macrophage-1 inhibitory cytokine (MIC-1) inhibit the trophoblast invasion process.

In preeclampsia, when trophoblast invasion failure results in hypoxia of the syncytiotrophoblast layer, this triggers cytotrophoblast cells to provide an adaptive response by stimulating the release of blood vessel growth factors such as angiogenic proteins. Among these factors include Vascular Endothelial Growth Factor (VEGF), Placental Growth Factor (PLGF), and Transforming Growth Factor β (TGF-β), one of which is Inhibin A [7].

Elevated serum levels of Inhibin A are detected in preeclampsia, and the increase usually begins around 10 weeks gestation, exceeding normal levels in well-progressing pregnancies.

Inhibin A and Activin A are glycoproteins and are beta-type Growth Factors [8, 9]. Both hormones, Inhibin A and Activin A, are produced in large quantities by the fetoplacenta during pregnancy. Inhibin A has a major role in regulating hormonal activity by providing negative feedback to gonadotropins, while Activin A participates in various biological processes in the body. In a normal pregnancy, levels of both tend to increase in the third

trimester, but in patients with preeclampsia (PE), it was found that levels of both can increase up to 10-fold, especially in cases of severe PE. Preeclampsia is often related to oxidative stress and systemic inflammation in the mother, which in turn can lead to increased production of Activin A [10, 11].

The important role of activin and inhibin during pregnancy is believed to be related to the fact that circulating levels of activin are generally very low or even undetectable under normal physiological conditions, except during pregnancy, when levels of inhibin, activin, and follistatin, likely all from the fetus and placenta, are significantly increased, especially during the third trimester of pregnancy. Follistatin concentrations during pregnancy are higher than activin concentrations, while basal inhibin levels tend to be high and decrease slightly before experiencing a sharp increase between the 25th and 30th weeks of pregnancy. Although the biological role of both during pregnancy has not been fully solved, abnormally low levels of inhibin in the mother's blood have been linked to the risk of miscarriage and other complications. On the other hand, abnormally elevated levels of activin in late pregnancy have been linked to the risk of preeclampsia, preterm labor, and gestational diabetes [12].

Conclusion

The administration of activin-A to the placenta under normal conditions, diabetes, and preeclampsia showed the lowest average in healthy mother conditions of 0.62 mIU / ml, followed by diabetic mother of 1.05 mIU / ml and preeclampsia of 1.23 mIU / ml. While inhibin-A shows an average in the placenta healthy mother conditions of 0.45 mIU / ml, followed by diabetes conditions of 0.97 mIU / ml and preeclampsia of 1.10 mIU / ml. Hence this concluded that placental activin-A and inhibin-A levels both in preeclampsia pregnancy have higher values than diabetes mothers.

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Conflict of interest: None

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Ethics statement: We declared that this research was conducted in accordance to Declaration of Helsinki and all procedures were carried out with understanding and informed consent of all subject.

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