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ORIGINAL ARTICLE

Inhibin A levels and severity of preeclampsia

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Abstract
Objective To evaluate the use of third trimester inhibin A levels to assess the severity of preeclampsia.
Materials and methods Blood samples were taken from women diagnosed with mild and severe preeclampsia during the third trimester of pregnancy. Blood samples were collected in plain tubes, centrifuged and stored at −80°C until analyzed. All serum samples were measured for inhibin A levels by enzyme-linked immunosorbent assays.
Results Inhibin A levels were greater in the severe (1,435.9 ± 603.2 pg/mL) than in the mild preeclampsia group (1,021.9 ± 438.8 pg/mL, $P = 0.014$).
Conclusion Inhibin A levels rise with increasing severity of disease. However, there is considerable overlap of serum inhibin A levels in women with mild and severe preeclampsia. Inhibin A is therefore not a useful adjunct for the classification of preeclampsia.

Keywords Inhibin A · Preeclampsia · Pregnancy · Severity

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Introduction

Preeclampsia is one of the most common complications in obstetrics. It can cause maternal and fetal morbidity and mortality [1]. The exact etiology is unknown, but it is associated with a failure of the trophoblastic invasion of the spiral arteries. An early detection of this complication may pave the way to an improvement in pregnancy outcome by increasing the patient's surveillance or allowing an early initiation of appropriate therapeutic interventions [11].

A variety of biochemical markers have been proposed for the purpose of predicting or assessing the development of preeclampsia. Inhibins, ones of the markers, are glycoprotein hormones that belong to the transforming growth factor β superfamily, consisting of $\alpha\beta_A$ (inhibin A) and $\alpha\beta_B$ (inhibin B) [6]. Corpus luteum is thought to be a source of inhibin A in pregnant women. Recent studies reveal the origin of inhibin A to be the feto-placental unit [3, 15]. Concentrations of circulating dimeric inhibin A rise in early pregnancy, fall after 12 weeks of gestation and remain low until the 24th week. Thereafter, the concentration increases gradually, but with a marked rise in the third trimester [9]. The serum inhibin A concentration may rise in preeclampsia because of abnormal trophoblastic invasion of the uterine vessels [14]. Recently, inhibin A has been evaluated for the prediction of preeclampsia and the assessment of severity [4, 8, 9, 16]. Previously, we found that serum inhibin A was higher in preeclampsia than in nomal pregnancy [10].

There has only been one study that compared inhibin A levels to the severity of hypertensive disorders in pregnancy [17]. The aim of this study was to evaluate the use of third trimester inhibin A levels in relation to the severity of preeclampsia.

Materials and methods

Subjects

This was a cross-sectional study at the Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand between April and December 2007. This study was approved by the Reseach Ethics Committee of the Faculty of Medicine. The protocol was explained to the participants and informed consent was obtained.

Subjects had no prior history of hypertension and had documented normal blood pressure during the first trimester. Patients with preeclampsia had newly diagnosed hypertension after 20 weeks of gestation. Preeclampsia was defined as a blood pressure of at least 140/90 mmHg measured on two occasions of 6 h apart, accompanied by proteinuria of at least 300 mg/24 h, or at least 1+ on dipstick testing [1]. Severe preeclampsia was defined as a condition with one or more of the following: blood pressure of at least 160/110 mmHg measured on two occasions of 6 h apart, proteinuria of at least 5 g/24 h, or at least 3+ on dipstick testing, oliguria of less than 500 mL/24 h, cerebral or visual disturbances, pulmonary edema or cyanosis, epigastric or right upper quadrant pain, impaired liver function, thrombocytopenia and fetal growth restriction [1]. Subjects were excluded if they suffered from chronic hypertension, diabetes, multifetal gestation, and renal or connective tissue disease. Blood was taken at diagnosis before intravenous fluid administration or any pharmacological treatments. Blood samples were drawn and collected in plain tubes and centrifuged at 3,000 rpm for 10 min. Serum was obtained for this study.

The sample size calculation was based on the inhibin A level in mild and severe preeclampsia obtained from our pilot study. Mean and standard deviation of inhibin A were 1,145 and 569 pg/mL in mild preeclampsia and 1,720 and 541 pg/mL in severe preeclampsia. Thus, we needed 21 women in each group to detect the statistical difference ($\alpha = 0.05$, $\beta = 0.1$).

Assay for inhibin A

Serum samples were stored at −80°C until analysis. Inhibin A level was measured in serum by means of two-site enzyme-linked immunosorbent assays (Diagnostic Systems Labolatories, Inc., TX, USA) according to the manufacturer's recommendations and as previously described [12]. The kit is an enzymatically amplified two-step sandwich-type immunoassay. The minimal detectable concentration in the assays for inhibin A reported by the manufacturer is 1 pg/mL. The interassay and intra-assay coefficients of variation were <10%.

Statistical analysis

The data were analyzed with the SPSS software package version 12.0 for Windows (SPSS Inc., Chicago, USA) and expressed in terms of mean, standard deviation, median, interquartile range and percentage. Continuous variables were compared with the student's *t* test or Mann–Whitney *U* test, while the χ^2 test (or Fisher exact tests when appropriate) was used to compare the frequencies of pregnancy outcomes. A *P*-value of <0.05 was considered to be statistically significant.

Results

A total of 52 pregnant women complicated with preeclampsia were recruited for the study period. A total of 23 women were diagnosed with mild preeclampsia and 29 women had severe preeclampsia. The baseline characteristics and neonatal outcomes of these women are presented in Table 1. Baseline characteristics in both the groups were similar with regard to maternal age, parity, number of total antenatal care visits, maternal height, maternal body mass index (BMI) before pregnancy and total weight gain. But, we found that gestational age was lesser in the severe preeclampsia group. The mean blood pressure of the severe

Table 1 Patient characteristics and neonatal outcomes

	Mild preeclampsia ($n = 23$)	Severe preeclampsia ($n = 29$)	*P* value*
Age (years)	29.8 ± 5.6	28.5 ± 5.7	0.410
Parity			
Nulliparous	17 (73.9%)	22 (75.9%)	0.871†
Gestational age (weeks)	37.8 ± 1.4	34.8 ± 3.6	<0.001
Total antenatal care visit (times)	8.3 ± 2.8	7.1 ± 3.7	0.194
Height (cm)	157.1 ± 5.8	155.8 ± 6.1	0.449
BMI (kg/m^2)	24.8 ± 5.1	22.7 ± 4.5	0.126
Total weight gain (kg)	18.0 ± 8.3	15.2 ± 6.8	0.188
Systolic BP (mmHg)	147.9 ± 6.2	168.5 ± 17.6	<0.001
Diastolic BP (mmHg)	94.6 ± 6.2	109.9 ± 10.6	<0.001
Birth weight (g)	3,160.4 ± 576.1	2,162.6 ± 854.4	<0.001
SGA	0	6 (20.7%)	0.028†
Apgar score at 1 min	8.7 ± 0.6	7.3 ± 2.8	0.021
Apgar score at 5 min	9.9 ± 0.2	8.9 ± 2.3	0.042

Results are shown as mean ± standard deviation or *n* (%)

SGA small for gestational age

* Student's *t* test was used

† Chi-squared test was used in this instance

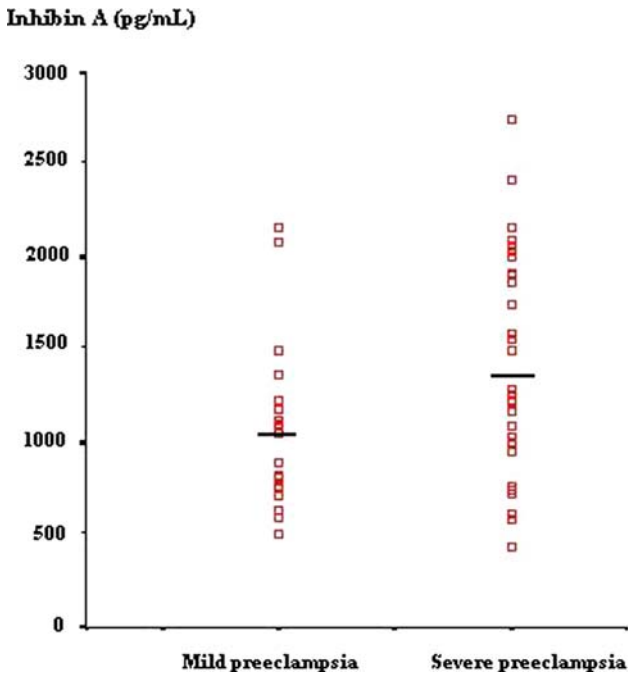

Fig. 1 Serum inhibin A for mild preeclampsia and severe preeclampsia

preeclampsia group was higher than that in the mild preeclampsia group (Table 1).

The mean levels of maternal serum inhibin A are shown in Fig. 1. The levels of inhibin A were significantly greater in the severe preeclampsia group than in the mild preeclampsia group (1,435.9 ± 603.2 pg/mL vs. 1,021.9 ± 438.8 pg/mL, $P = 0.014$). Median of the maternal serum inhibin A was significantly higher in the severe preeclampsia group than in the mild preeclampsia group ($P < 0.05$; Table 2). The levels of serum inhibin A in severe and mild preeclampsia group were 1.79 and 1.24 MOM, compared to normal pregnant women (Table 2).

Considering the neonatal outcome, the mean Apgar scores at 1 and 5 min and mean neonatal birth weight were significantly lesser in the severe preeclampsia group. The number of small for gestational age infants was higher in the severe preeclampsia group than in the mild preeclampsia group (Table 1).

Table 2 Median and interquartile range of serum inhibin A between mild preeclampsia and severe preeclampsia

Serum inhibin A (pg/mL)	Normal ($n = 30$)	Mild preeclampsia ($n = 23$)	Severe preeclampsia ($n = 29$)
Median	722.8	893.6*	1290.0*†
Interquartile range	423.6, 1,058.6	715.2, 1,182.4	974.1, 1,956.9
MOM	1	1.24	1.79

MOM multiple of median

* $P < 0.05$ when compared to normal

† $P < 0.05$ when compared to mild preeclampsia

Discussion

In this study, we found that levels of inhibin A were greater in the severe preeclampsia group than in the mild preeclampsia group. The pathophysiology of preeclampsia remains not fully known. Our observation is consistent with the hypothesis that inhibin A may be a manifestation of maternal disease and may play a role in the pathogenesis of the maternal response in preeclampsia [5]. There is evidence for increased proliferation of the underlying cytotrophoblast in preeclampsia [2]. This may be due to repair of ischemic damage to the surface syncytiotrophoblast. These processes of damage and repair may cause the functional alteration of a surface layer of syncytiotrophoblast in the preeclampsia placenta and may explain the increase in concentration of these biochemical markers [13].

Inhibin A levels were affected by gestational age. Inhibin A levels have a biphasic pattern during pregnancy, with the first peak at 8 weeks' gestation, a plateau between 14 and 30 weeks' gestation and a rise with a secondary peak at term [7]. Although gestational age was lesser in the severe preeclampsia group in this study, the higher level of inhibin A was not due to the gestational age effect.

We found that levels of inhibin A were greater in the severe preeclampsia group. This result was similar to previous reports [17]. In this study, although there was a significant increase in the severe preeclampsia group, there was an overlap between severe preeclampsia and mild preeclampsia, as in a previous study [17]. We confirmed with the previous study [17] and found that inhibin A levels were not useful to differentiate severe from mild preeclampsia, due to overlap of serum levels in women with severe and mild preeclampsia.

Muttukrisma et al. [8] reported that inhibin A levels were significantly increased in preeclampsia with no overlap levels measured in normal pregnancies. Silver et al. [16] studied inhibin A levels in preeclampsia or gestational hypertension compared with matched normotensive controls. Although inhibin A levels were significantly higher in women with preeclampsia, there were overlap levels with other study groups. The authors in both studies did not classify the severity of preeclampsia as in this present study.

Baseline characteristics in our control and study groups were similar except for gestational age at diagnosis. This was found to be lesser in the severe preeclampsia group. and may be explained by the greater severity of the disease in the severe preeclampsia group.

In conclusion, inhibin A levels rise with increasing severity of disease. There is considerable overlap of serum

inhibin A levels in women with mild and severe preeclampsia. Inhibin A is therefore not a useful adjunct for the classification of preeclampsia.

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Conflict of interest statement None.

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