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ORIGINAL ARTICLE

First trimester serum inhibin A in normal pregnant women

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Abstract
Objectives To establish reference ranges for maternal serum inhibin A in normal first trimester pregnant women.
Materials and methods This was a cross-sectional study. We measured maternal serum inhibin A in normal pregnant women gestation age between 6^{+0} and 14^{+6} weeks using the enzyme-linked immunosorbent assay (ELISA) method. Maternal serum inhibin A was analyzed according to gestational ages (GA).
Results Serum of 300 pregnancies was analyzed and the outcome demonstrated the median of maternal serum inhibin A according to gestational age. The levels of maternal serum inhibin A during the 6^{0}–6^{+6} week of gestations are lowest when compared with other gestational age. The levels of maternal serum inhibin A during 9^{0}–9^{+6} week of gestations are maximal. Maternal serum inhibin A then declined until 14 weeks of gestation.
Conclusion Serum inhibin A can be measured during the first trimester of pregnancy by using the recent ELISA technique. Our reference ranges might be useful for further studies, such as prediction of adverse pregnancy outcome in threatened abortion.

Keywords Serum inhibin A · First trimester · Pregnancy · Normal · ELISA

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Introduction

Inhibins are glycoproteins produced by the granolosa and theca cells of the ovary and by the Sertoli cells of the testis. Inhibin is a dimeric disulfide-linked glycoprotein molecule, consisting of α and β subunits [4]. All inhibins share a common α subunit (18–20 kDa), but depending on the type of β subunit [βA (13 kDa) and βB (15 kDa)], inhibin is classified as inhibin A or B. Apart from inhibin A or B, these subunits are also present in circulation in large dimeric or monomeric forms [16].

During pregnancy, serum inhibin A can be measured in maternal serum in significant concentration during pregnancy and the level increases as gestational age advances because inhibin A is produced from human placenta and fetal membranes [9, 13]. Although the precise spectrum of functions of these hormones in pregnancy has not been fully delineated, abnormal levels have been noted in association with maternal complications of pregnancy, such as miscarriage, preeclampsia and preterm labor. Inhibin A has been used as a marker for fetal abnormality, Down syndrome [11, 17]. There are studies which demonstrated that maternal serum inhibin A levels in women presenting with signs and symptoms of miscarriage (abdominal pain and/or vaginal bleeding) were significantly lower in these women who had a miscarriage confirmed, whether it was complete or incomplete, compared with those women who had an ongoing viable pregnancy [10, 14, 15]. For using inhibin A as a marker of Down syndrome and prediction of miscarriage, normal levels of inhibin A in first trimester of pregnancy are required. However, there have been no reports on the baseline level of inhibin A in normal Thai pregnant women classified in each week of gestation age during first trimester. Thus, the objective of this study was to establish reference ranges for the first trimester maternal serum inhibin A level of Thai pregnant women.

Materials and methods

Subjects

The study was conducted as a prospective descriptive cross-sectional study including 300 pregnancies between 6^{+0} and 14^{+6} weeks according to their last menstrual period (LMP) who underwent antenatal care at Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. Informed consent was obtained from each participant, and the Ethics Committee of the faculty has approved this study. Inclusion criteria were (1) singleton gestation, (2) accurate dating based on LMP and calculated gestational age (GA) by crown-rump length (CRL) measurement was in agreement, and (3) have a term delivery with normal birth weight fetus. The exclusion criteria were (1) vaginal bleeding during pregnancy, (2) pregnancy complications (e.g. diabetes, hypertensive disorders), (3) miscarriage or fetal demise, (4) fetus with structural or chromosomal abnormalities, (5) fetus with growth restriction or macrosomia, and (6) lost to follow-up.

Study procedures

Five milliliter of blood sample was collected from each subject via vacuum tubes. The blood was allowed to clot. The samples were then centrifuged at 3,500 round per minute (rpm) for 10 min. The sera were separated and stored at −80°C until assayed. In each pregnant woman, the gestational age was confirmed by measuring her fetal crown-rump length (CRL) using an Aloka model Prosound 5000 (Aloka, Tokyo, Japan) ultrasound machine with a 7.5 MHz vaginal- or a 3.75 MHz abdominal transducer. CRL was measured from the cranial to the caudal end of the body with the fetus in neutral position. All fetal heartbeats were confirmed during ultrasound measurement. All newborns were proved to be normal at birth. Inhibin A was measured in duplicate using a commercial sandwich enzyme-linked immunosorbent assay (ELISA) kit (Diagnostic System Laboratories, TX, USA) according to the manufacturers' protocol. The limit of sensitivity for inhibin A was <1 pg/ml. The inter- and intra-assay coefficients of variation were <10%.

Statistical analysis

Statistical analysis was performed with SPSS software package version 11.0 (SPSS, Chicago, IL, USA). Mean and standard deviation (SD) was used for maternal characteristic. Since the frequency distributions of inhibin A level was not normally distributed, we described our data as median and range (minimum, maximum) rather than mean and SD.

Serum inhibin A levels were also computed at weekly intervals for GA.

Results

During the study period, 300 samples from 300 pregnancies were recruited. There were no cases that lost to follow-up. The mean ± standard deviation (SD) of age was 29.3 ± 5.7 years. Maternal serum inhibin A level according to GA is presented in Table 1 and Fig. 1.

The median of maternal serum inhibin A in normal pregnant women during the first trimester was 391.5 (ranged 29–1415.1) pg/ml. The lowest maternal serum inhibin A level was demonstrated at the 6^{0}–6^{+6} week of gestation. After the sixth week of gestation, inhibin A continued to increase to peak around 9^{0}–9^{+6} weeks of gestation. During late first trimester, pattern of serum inhibin A declined slowly until 14 weeks of gestation.

Discussion

This study demonstrates that the level of serum inhibin A can be measured during the first trimester of pregnancy by

Table 1 Maternal serum inhibin A level according to gestational age

Gestational age (weeks^{+days})	*N*	Median (min–max) (pg/ml)	10 percentile (pg/ml)	90 percentile (pg/ml)
6^{+0}–6^{+6}	24	172 (29–820.2)	45.3	484.9
7^{+0}–7^{+6}	42	491.1 (61.5–1,202.2)	260.1	901.1
8^{+0}–8^{+6}	31	499 (172.4–1138.9)	212.2	1050.9
9^{+0}–9^{+6}	41	547.6 (221.7–1109.8)	271.9	888.4
10^{+0}–10^{+6}	40	482.8 (168.9–1,296.4)	212.1	1009.5
11^{+0}–11^{+6}	34	371.4 (839–950.5)	173.3	616.7
12^{+0}–12^{+6}	36	354.8 (106.4–1,027.6)	199.0	696.5
13^{+0}–13^{+6}	33	267.5 (82.6–1,415.1)	135.4	542.6
14^{+0}–14^{+6}	19	255.2 (127.5–975.1)	152.2	544.7

SD standard deviation

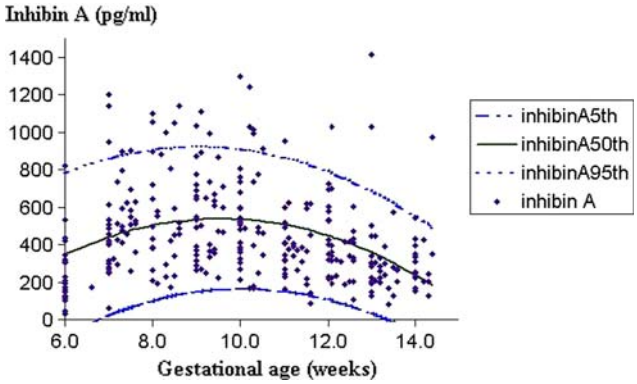

Fig. 1 Maternal serum inhibin A levels according to gestation age

using the ELISA technique. The median of maternal serum inhibin A was lowest at the 6^0–6^{+6} weeks of gestation. The maximal median of maternal serum inhibin A can be demonstrated at the 9^0–9^{+6} weeks of gestation. The increasing level of serum inhibin A occurs during pregnancy was a result of the production from human placenta and fetal membranes [7, 11, 16, 18].

From this study, we found that maternal serum inhibin A increased from the 6^0–6^{+6} weeks of gestation to the maximal level at the 9^0–9^{+6} weeks of gestation. Then it gradually decreased until the 14th week of gestation. This finding is consistent with other previous studies [3, 10, 18]. However, in the present study, we have more subjects than the earlier studies [3, 10, 18]. In the present study, the measurements were made using the specific two-site enzyme immunoassays for dimeric inhibin A as in the previous studies [3, 12], and the data show that inhibin A is predominantly a production of fetoplacenta in early pregnancy.

Inhibin A concentrations rapidly increase until the 9th- or 10th week of gestation, and then falls and gradually raises again throughout the third trimester. This suggests that inhibin A may have differing functions throughout pregnancy [3]. Inhibin A may prove to be a marker for fetal or placental abnormalities in pregnancy. In the first trimester, inhibin A has a role as a marker for early pregnancy viability. Its measurement might be able to predict pregnancy outcome in cases of recurrent miscarriage and threatened abortion [2, 8, 14, 16]. In the second trimester, it may be a useful marker to predict the risk of preeclampsia, preterm delivery and fetal growth restriction [6, 17]. It has also been shown to be useful in screening for fetal karyotypic abnormalities [1, 5, 11].

In conclusion, serum inhibin A can be measured during the first trimester of pregnancy by using the recent ELISA technique. Our reference ranges for the first trimester serum inhibin A might be served as a normative data of normal pregnant women. It might be useful for further prospective studies in two viewpoints: first, for prediction of adverse pregnancy outcome such as miscarriage, preeclampsia or fetal growth disorders and second, as a serum marker for fetal aneuploidy screening.

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