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Research article

A comparison between serum inhibin A levels in pre-eclampsia and normotensive pregnancy

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ABSTRACT

Aim: To evaluate the validity of serum inhibin A levels in assessing the severity of preeclampsia. **Methods:** Hospital based, prospective study conducted in Kasturba Medical College, Mangalore. **Inclusion criteria:** The patients in the study will be divided into cases and controls based on the criteria proposed. 5mL of venous blood was collected from each patient in an aseptic plain and EDTA vacutainer. Serum inhibin A levels estimated by the ELISA method. **Statistical analysis:** The samples were statistically analysed by [chi-square] χ^2, student's t-test. Mann-Whitney U-test was used for the comparison of multiples of median. All tests were two-sided.Statistical significance was inferred for *P* values <0.05. **Results:** 72 patients were studied. 36 women were preclampsia cases and 36 were controls, were also divided in to subgroups mild and severe preeclampsia. The median value of inhibin A level in normotensive controls was 901.4pg/mL while in mild pre-eclampsia patients was 1125pg/mL (p>0.05), which was statistically not significant while median serum inhibin A level in severe pre-eclampsia was 1472.5pg/mL (p <0.05), which was statistically significant. **Conclusion:** There is increase in the serum inhibinA levels in pre-eclampsia group when compared to that in normotensive women. The severe pre-eclamptic sub group patients had statistically significant rise of MOM [p<0.05] compared to that of normotensive controls, there is considerable overlapping of serum inhibin A values among cases and controls. Further studies are needed to prove whether serum inhibinA levels can be used for prediction of pre-eclampsia in India.

Key words: ELISA, Inhibin A , Pre-eclampsia, Pregnancy

1. INTRODUCTION

Pre-eclampsia is one of the most common complications in obstetrics. The exact etiology is unknown, but it is associated with a failure of the trophoblastic invasion of the spiral arteries. Current hypothesis is that pre-eclampsia is a two stage disorder, stage 1 caused by faulty endovascular trophoblastic remodeling that downstream causes the stage 2 clinical syndrome [1]. 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 [2].

A variety of biochemical markers have been proposed for the purpose of predicting or assessing the development of preeclampsia. Inhibin, one of the markers, is a glycoprotein hormone that belongs to the transforming growth factor - superfamily, consisting of $\alpha\beta_A$ (inhibin A) and $\alpha\beta_B$ (inhibin B) [3]. Corpus luteum was 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 [4]. There is also evidence for altered levels of these hormones in the blood of women affected by chromosomal abnormality, miscarriage and foetal growth restriction in pregnancy [5-9]. Women with pre-eclampsia have distinctively high levels of activin A, inhibin A, and pro αC [10]. We therefore will measure the levels of inhibin A in normotensive women and in those with pre-eclampsia, and study whether this protein levels can be correlated with severity of pre-eclampsia.

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The main aim of the present study is to evaluate the validity of serum inhibin A levels in assessing the severity of preeclampsia. The broad objectives of the study are to (i) measure the serum inhibin A levels in the normotensive and pre eclamptic patients and compare it with the controls and (ii) analyse if the inhibin A levels are significantly correlating with the severity of preeclampsia.

2. MATERIALS AND METHODS

2.1. Study protocol

(i) *Type of study*: Hospital based, prospective study
(ii) *Period of study*: I Year; From 25-4- 2010 till 25-4-2011
(iii) *Place of study*: Lady Goschen Hospital, Mangalore and Kasturba Medical College Hospital, Attavar, Mangalore
(iv) *Inclusion criteria*:

- Pregnant women visiting the above hospitals, who meet the following criteria, will be included in the study.
- The patients in the study will be divided into 2 groups as cases and controls based on the following criteria and will be studied further.

(v) *Cases*:

- Pregnant women in second and third trimester diagnosed to have pre-eclampsia with or without complications, not in labor, of any age and parity.
- Pre-eclampsia defined as recording of blood pressure measure of >/=140/90mmHg [right arm sitting position] in pregnant women of >20 weeks period of gestation, atleast during 2 occasions, 6 hours apart on bed rest ,with proteinuria [>/= 300mg proteinuria in 24h urine collection or >/= 1+ proteinuria on urine dip stick test] and with/without edema.

  Pre-eclampsia is further divided into 2 sub groups, as follows:

  Severe pre-eclampsia: Pre-eclampsia with any of the following features,

  - Blood pressure: 160mmHg or higher systolic or 110mmHg or higher diastolic on two occasions at least six hours apart in a woman on bed rest.
  - Proteinuria: 5g or more of protein in a 24h urine collection or 3+ or greater on urine dipstick testing of two random urine samples collected at least four hours apart.
  - Oliguria: less than 500mL of urine in 24h.
  - Visual disturbances
  - Pulmonary edema or cyanosis
  - Epigastric or right upper quadrant pain
  - Impaired liver function
  - Thrombocytopenia
  - Intrauterine growth restriction

  Mild pre-eclampsia:

  - All the cases of pre-eclampsia not fulfilling the criteria for severe pre-eclampsia

(vi) *Controls*: Normotensive pregnant women in second or third trimester matched for age (+/-1year), parity and period of gestation (+/-1week) with that of cases.
(vii) *Exclusion criteria*:

- Pregnant women of any trimester in labor
- Pregnant women of first trimester
- Non pregnant women
- Women belonging to control develop pre-eclampsia concurrently.
- Women with hypertension [>/=140/90mmHg] but with no proteinuria.

2.2. Biochemical measurements

After the woman signs the written, informed consent form, 5ml of venous blood was collected from each patient in an aseptic plain and EDTA vacutainer. Samples were immediately taken to lab and centrifuged to obtain plasma, stored at -4°C in the Kasturba Medical College Hospital, Ambedkar Circle Laboratory, Mangalore. Serum inhibin A levels will be estimated by the ELISA method. The other tests including peripheral smear, platelet count, urine protein levels, liver and renal function tests were all performed in the same laboratory.

2.3. Statistical analysis

The samples were statistically analysed by [chi-square] χ^2, student's *t*-test. Mann-Whitney U-test was used for the comparison of multiples of median. All tests were two-sided.The data was expressed in terms of mean, median, percentage. Statistical significance was inferred for $P < 0.05$.

3. RESULTS

In the present study a total of 72 patients were studied. All patients in the study were divided into 2 groups as cases and controls. 36 were preclampsia cases and 36 patients were controls. Of the 36 pre-eclampsia patients 14[38.8%] patients belonged to sub group-severe pre-eclampsia as per the inclusion criteria and 22[61.1%] patients had mild preeclampsia. The controls studied were chosen by matching their age, parity and also period of gestation to the study group. Accordingly, the mean age group of cases was of 25.9 years and that of controls being 26.2 years which were comparable. The average gestational age of cases was 36 weeks and 4 days while that of controls were 36 weeks and 5 days which were comparable.

Out of 72 subjects studied, 58.3%(42) were primigravida, while others were multigravida. 2 of them (2.8%) were grand multipara women. The mean inhibin A value of the cases were 1373pg/mL and that of controls were 1160.2pg/mL which was statistically not significant.

The median value of inhibin A level (Table a) in normotensive controls was 901.4pg/ml while in mild pre-eclampsia patients was 1125pg/mL(p>0.05), which was

statistically not significant while median serum inhibin A level in severe pre-eclampsia was 1472.5pg/mL($p<0.05$) ,which was statistically significant. The multiples of median [MOM] (Table 1, Fig.1) of severe pre-eclampsia sub group was 1.63, a statistically significant elevation [$p<0.05$] compared to that of controls in whom MOM was 1. In the sub group mild pre-eclampsia MOM was 1.24 which was statistically not significant.

There was overlapping of inhibin A levels among cases as well as controls (Fig.2). Overlapping of serum inhibin A levels among mild and severe pre-eclampsia sub-groups was also observed in our study (Fig.3).

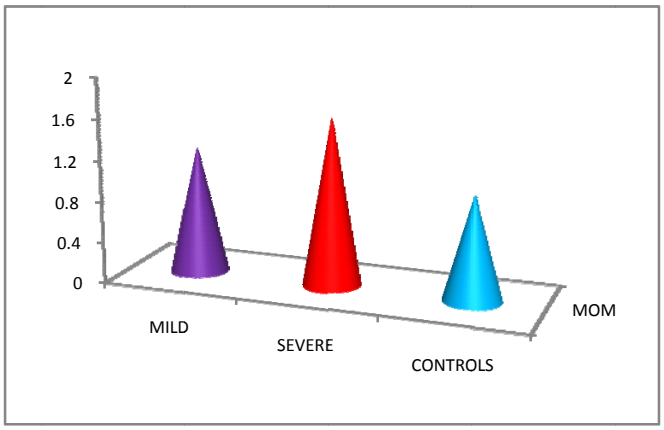

Fig.1.MOM of inhibin A levels in the study

Table 1
Median value & mom of inhibin A levels in the study

Type	Median [pg/mL]	MOM
Mild	1125	1.24
Severe	1472.5	1.63*
Controls	901.4	1

*Statistically significant (P<0.05)

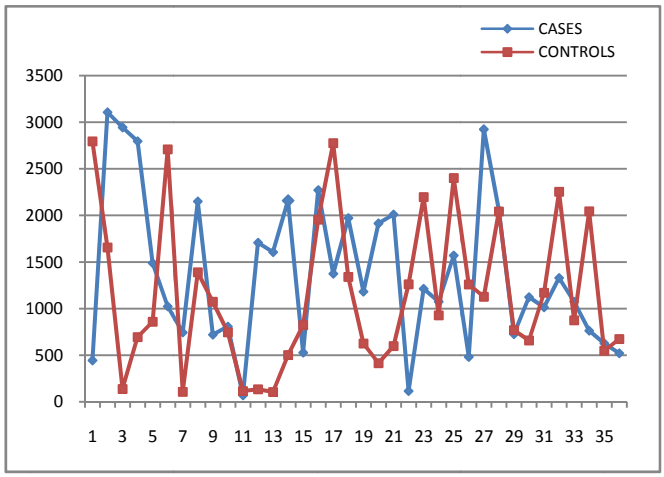

Fig.2. Inhibin A levels of cases and controls

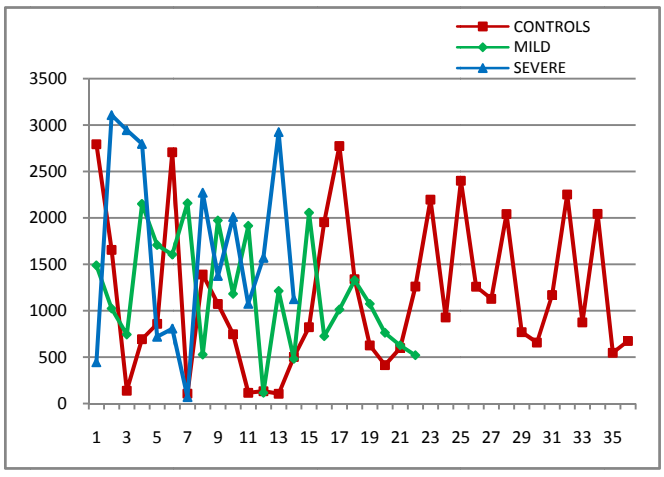

Fig.3. Inhibin A values of controls and sub groups

4. DISCUSSION

Pre-eclampsia is a syndrome which develops during pregnancy. In preeclampsia, there is partial or complete failure of trophoblastic invasion of the myometrial segments of the spiral arteries, causes ischaemic damage to the syncytiotrophoblast. The damage and repair processes may cause the functional alteration of the surface layer of syncytiotrophoblast in pre-eclampsia placenta and may explain the increase in concentration of inhibin A in the maternal circulation [11].

In this study, we compared 36 pre-eclamptic cases with 36 normotensive controls which were matched for gestational age, parity and maternal age. We found that mean serum inhibin A levels were greater in the pre-eclampsia patients (1373pg/mL) than in the normotensive controls (1160.2pg/mL) but it was not statistically significant. There are other studies which found mean serum inhibin A levels higher than normotensive controls and also were found to be statistically significant. Muttukrishna *et al* [12] studied inhibin A levels in 20 women with pre-eclampsia and 20 women with normal pregnancies, they were matched for gestational age,parity and maternal age. Serum Inhibin A levels were significantly increased in the serum of preeclamptics. They found mean serum inhibinA level of normotensives was 0.36ng/mL while that of preeclamptics was 3ng/mL.

The study by H. Laivuori *et al* [13] done in pregnant women of third trimester confirmed that activin A, inhibin A, and pro – αC are markedly elevated in preeclampsia. The mean serum inhibin A level of normotensive group was 882ng/L while that of preeclamptic group was found to be 1691ng/L [$p<0.03$]. He also found that the elevations are related to the amount of proteinuria [$P<0.02$]. The diagnostic sensitivity of inhibin A was 73%. Pre-eclamptic changes in uteroplacentaltissues, rather than renal changes, are primarily responsible for the elevations of these proteins in serum [13]. Krissada *et al* [14] found that mean serum inhibin A levels in pre-eclampsia patients [1229pg/mL] was significantly higher [$p=0.002$] compared to normotensives [839pg/mL].

In the study by Muttukrishna *et al* [15], he had found that the levels of serum inhibin A levels were 3-6 fold higher in uterine and peripheral vein samples and 25 fold higher in urine samples, in patients who developed pre-eclampsia before 37weeks period of gestation compared to controls [p<0.001]. They found 3-4 fold higher in uterine and peripheral vein samples and 12 fold higher values of inhibin A in urine samples, in patients who developed pre-eclampsia after 37 weeks period of gestation compared to controls. The mean increase in the inhibin A in early onset severe pre-eclampsia disease was higher compared to that seen in patients presenting at more than 37 weeks of gestation but was not statistically significant. It suggests that magnitude of rise is the result of severity of the disease and not the stage of gestation at which it develops. However he also concluded that magnitude of rise in inhibin A in urine suggests that the urinary measurements may be more discriminative than peripheral blood levels, and this may be a better screening test.

In a study done in India by Meena *et al* [16] she recognized a significant positive correlation between second trimester serum markers and development of pre-eclampsia (p<0.001). In the 50 antenatal women studied a significant rise of mean serum mean inhibin-A level (1248.49pg/mL, >2.0MoM, P<0.001) was present in those who developed preeclampsia. Their study concluded that with the second trimester serum marker study, prediction of pre-eclampsia is possible at incipient stage and its adverse pregnancy outcome can be minimized.

The other finding in our study we found was that there is positive correlation between serum inhibin A levels and occurrence of severe preeclampsia. The MOM of inhibin A level of severe pre-eclampsia patients was (1.63) compared to that of normotensive controls (1) which was statistically significant [p<0.05]. This finding was similar to that of Vorapong *et al* [17], who had studied use of inhibin A in the third trimester to assess severity of pre-eclampsia. He had found that inhibin A levels rise with increasing severity of disease. MOM of inhibin A levels were 1.24 and 1.79 compared to normotensive women in mild and severe pre-eclampsia respectively. Median of serum inhibin A levels in severe pre-eclampsia group was significantly higher than that in the mild pre-eclampsia group.

Cuckle *et al* [18] studied 28 women, at 13-18 weeks period of gestation, and found that a statistically significant elevation of inhibin A levels (2.01MOM) in the cases who had subsequently developed pre-eclampsia and concluded that maternal serum inhibin A levels can be increased months before the onset of symptoms, which provides an opportunity to study the early natural history of the disease and possibly to conduct treatment trials.

In the present study, overlapping of the inhibin A levels among pre-eclampsia and controls were observed. Hence this test may not be useful adjunct in the diagnosis ofpreeclampsia. Silver *et al* [19], studied inhibin A levels in pre-eclampsia or gestational hypertension and compared with matched normotensive controls, found overlapping of serum inhibin A levels with that of the controls. In this study, although there was significant increase in the serum inhibin A levels in severe pre-eclampsia group, there was an overlap between the severe and mild pre-eclampsia subgroups. So inhibin A levels are not useful to differentiate severe from mild preeclampsia. Overlapping of serum inhibin A levels in mild and severe preeclamptic patients was also observed in studies by Krissada *et al* [14], Vorapong *et al* [13] and Zeeman *et al* [20]. Differences in stage of pre-eclampsia or in genetic background or in the sample sizes in these studies may explain the discrepencies [13].

As suggested by Cuckle *et al* [18], a simple algorithm could be devised, as is standard practice with Down's syndrome screening to calculate the risk of adverse outcome given the predisposing factors and the biochemical marker levels. As in India, the use of quadraple test as a screening method for detection of anomalies in early pregnancy is rising, further studies are required to implicate use of inhibin A levels as a predictor for severe preeclampsia.

5. CONCLUSIONS

In our study, although the severe preeclamptic sub group patients had statistically significant rise of MOM [p<0.05] compared to that of normotensive controls, there is considerable overlapping of serum inhibin A values among cases and controls, so also among mild and severe preeclamptic sub groups. So serum inhibin A level may not be a useful adjunct for the classification of preeclampsia. Further studies are needed to prove whether serum inhibin A levels can be used for prediction of pre-eclampsia in India, as early detection and management would improve the maternal and neonatal outcome.

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