SERUM INHIBIN A LEVELS IN NORMAL PREGNANCY AND PREECLAMPSIA AND RELATION TO ITS SEVERITY

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ABSTRACT

Background: Preeclampsia, more than just being proteinuric hypertension in pregnancy, is a state of exaggerated systemic inflammation and remains a leading direct cause of maternal morbidity and mortality.

Objectives: To compare the levels of inhibin A in patients with Preeclampsia and in normal pregnancy and to correlate the severity of preeclampsia with the levels of inhibin A.

Results: Majority of the cases were in the age group of 21-25 years (48%) and the incidence of preeclampsia was more among the Primigravida (64%). The mean gestational age in the study group was 36.97±2.98 weeks. Among the cases, 48% belonged to the mild preeclampsia and 52% to the severe preeclampsia subgroup. The mean S.inhibin A levels were 1053.55± 217.77, 1488.92±73.91 and 947.07±165.05 pg/ml in the mild preeclampsia, severe preeclampsia and control group respectively with statistically significant p values (**p<0.001** between cases & controls, **p<0.001** between mild & severe preeclampsia subgroup, **p<0.05** between mild preeclampsia and control group). IUGR, prematurity and still birth were seen to be more associated with the preeclampsia group when compared to control group. Complications like eclampsia, abruption, thrombocytopenia and pulmonary edema were noted among the preeclampsia group.

Conclusion: There is a statistically highly significant difference in the S.inhibin A levels between preeclampsia cases and normotensive controls and there is a rise in S.inhibin A

levels with increasing severity of the disease. There was a significant difference in the mean S.inhibin A levels in mild preeclampsia and control group but considerable overlap in the values was seen. Hence, S.inhibin A levels can serve as an useful adjunct, though not a sole indicator, to grade the severity of the disease as early detection and management would improve maternal and neonatal outcome.

Keywords : Inhibin A, Preeclampsia, Normal pregnancy.

INTRODUCTION:

Preeclampsia is defined as pregnancy specific syndrome that can virtually affect every organ system. From Public health perspective, the condition complicates 6-8% of pregnancies, 10% of first pregnancies and 20-25% of women with chronic hypertension.[1] Globally 10-15% of maternal deaths that occur every year are associated with hypertensive disorders of pregnancy. The exact cause of preeclampsia remains inconclusive, but it is known to be multifactorial, with the placenta taking the center stage.[2] Several placental biomarkers have been tried for predicting the development and assessing the severity of preeclampsia.[3]

Inhibin is one of the placental markers. Inhibin is a glycoprotein which belongs to the transforming growth factor superfamily and consists of Inhibin A and Inhibin B.[3]

Inhibin A is mainly produced by the syncytiotrophoblast of the human placenta. Failure of trophhoblastic invasion causes ischaemic damage to the syncytiotrophoblast leading to functional alteration of its surface and this surface alteration is considered as the contributory factor for increased ‘leakage’ of inhibin A into maternal circulation.[5,6,7]

METHODS:

In the present study, a total number of 100 pregnant women were included out of which 50 were preeclampsia (cases) and 50 were normotensive pregnant women (control) who attended the Department of Obstetrics and Gynecology at R L Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Academy Of Higher Education, Tamaka, Kolar between January 2012 to July 2014. It was a case control study.

Inclusion Criteria:

Pregnant women fulfilling the following criteria. The patients were divided into cases and controls.

Cases- Pregnant women >20 weeks of gestation diagnosed with preeclampsia of any age and parity. Preeclampsia is defined as blood pressure of ≥140/90 (right arm sitting position) in pregnant women >20 weeks gestation, atleast on 2 occasions, 6 hours apart on bed rest, along with proteinuria (≥ 300 mg proteinuria in 24h urine or ≥ 1+ proteinuria on dipstick method). They were further divided into severe and mild preeclampsia.

Controls- Normotensive pregnant women >20 weeks gestation, with matched age (+/- 1 year), period of gestation (+/- 1 week), and parity with those of the cases.

Exclusion Criteria

- Women with associated conditions as gestational diabetes mellitus
- Pregnant women with hypertension but without proteinuria
- Pregnant women <20 weeks gestation

Methodology: 5 ml of venous blood was drawn in a plain EDTA vacutainer. It was centrifuged for 10 minutes at 3000 rpm so as to separate out 2 ml of the serum. The serum was collected in aliquot tube and stored in the freezer at -8ºC till analysis. Serum inhibin A levels were estimated by Chemiluminescent Immunoassay. The various other investigations

which were done were complete blood count, renal function tests, liver function tests, urine protein, coagulation profile and fundoscopy. Fetal ultrasonography with doppler, if required.

The statistical analysis used were:

- Descriptives – mean, median, quartiles, standard deviation;
- Frequency tables with graphs
- One sample t-test
- One way ANOVA with Tukey's multiple comparisons test

Analysis was done with licensed SPSS 19.0 software

RESULTS:

The present study was carried out from January 2012 to July 2014 to know the S.inhibin A levels in preeclampsia and normal pregnancy. A total of 100 patients were studied and results obtained are presented here under.

Table 1: Age distribution of the subjects under the study groups

Age in years	Cases		Controls	
	N	%	N	%
< 20	14	28	10	20
21-25	24	48	30	60
26-30	10	20	9	18
> 30	2	4	1	2
Total	50	100	50	100
Mean±SD	23.46±3.558		23.44±2.984	

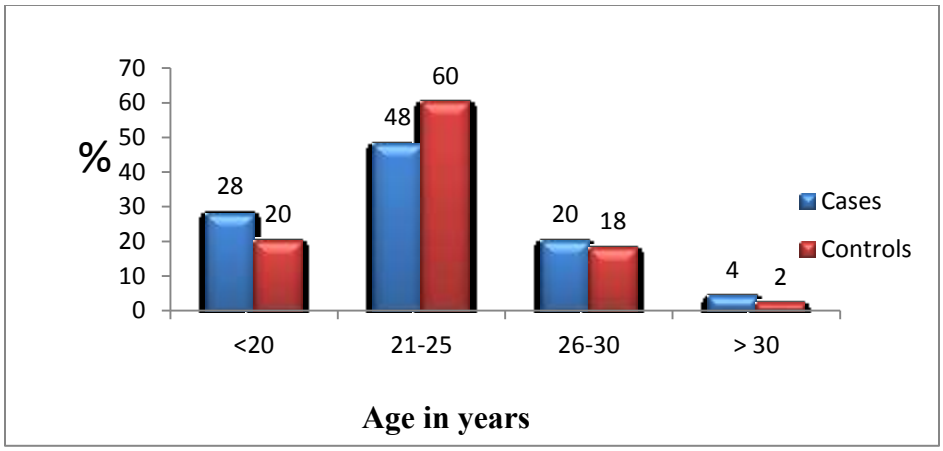

Chart 1: Multiple bar diagram showing the details of age distribution of the subjects under the study groups

The mean age among the pre eclampsia (cases) group was 23.46±3.558 and the mean age among the normotensive (controls) group was 23.44±2.984.

The cases & controls were matched for their parity. Among the subjects studied, 64% were primigravida and 36% were multigravida (Gravida 2 were 26% and Gravida 3 were 10%).

Table 2: Gestational age distribution of the subjects under the study groups

Gestational Age (weeks)	Cases		Controls	
	N	%	N	%
28.1-31	4	8	2	4
31.1-34	5	10	6	12
34.1-37	11	22	9	18
> 37	30	60	33	66
Total	50	100	50	100
Mean±SD	36.97±2.98		37.19±3.01	

The mean gestational age in the cases was 36.97±2.98 weeks and in the controls was 37.19±3.01 weeks

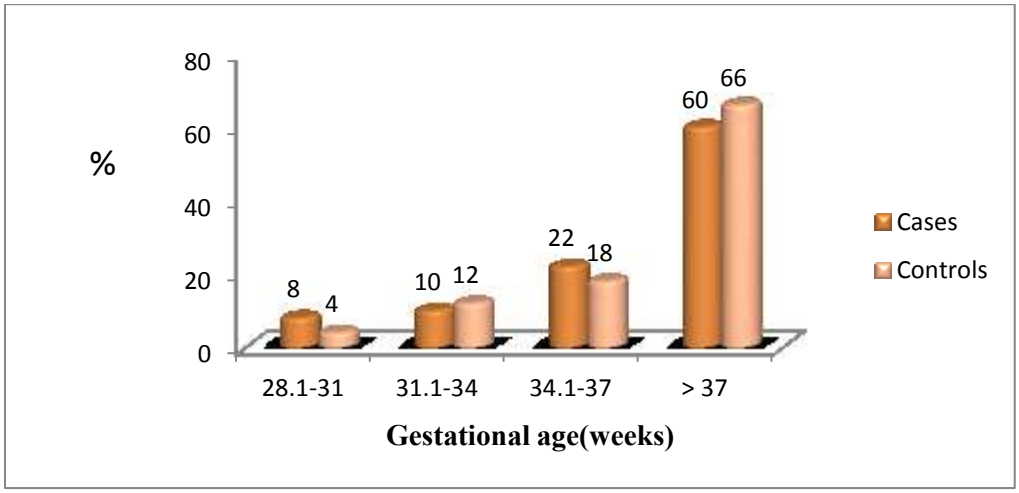

Chart 2: Multiple bar diagram showing gestational age distribution under the study groups

Among the preeclampsia group 52% belonged to severe preeclampsia group while 48% belonged to mild preeclampsia group.

Table 3: Comparison of S.inhibin A levels between Preeclampsia (cases) group & Normotensive (controls) group

	N	Mean(pg/ml)	Std. Deviation	Median(pg/ml)	25th Quartile	50th Quartile	75th Quartile
Cases	50	1279.95	270.78	1301.4	1131.075	1301.4	1520.2
Controls	50	947.07	165.05	923.5	842.675	923.5	1100.5

The above shows that the mean value of S. inhibin A among the cases was 1279.95±270.8 pg/ml and among the controls was 947.07±165.05 pg/ml. The median value among the cases was 1301.4 pg/ml and among the controls was 923.5 pg/ml. The p value is < 0.001**. Hence, there

is difference in S.inhibin A value between the cases & controls which is statistically highly significant

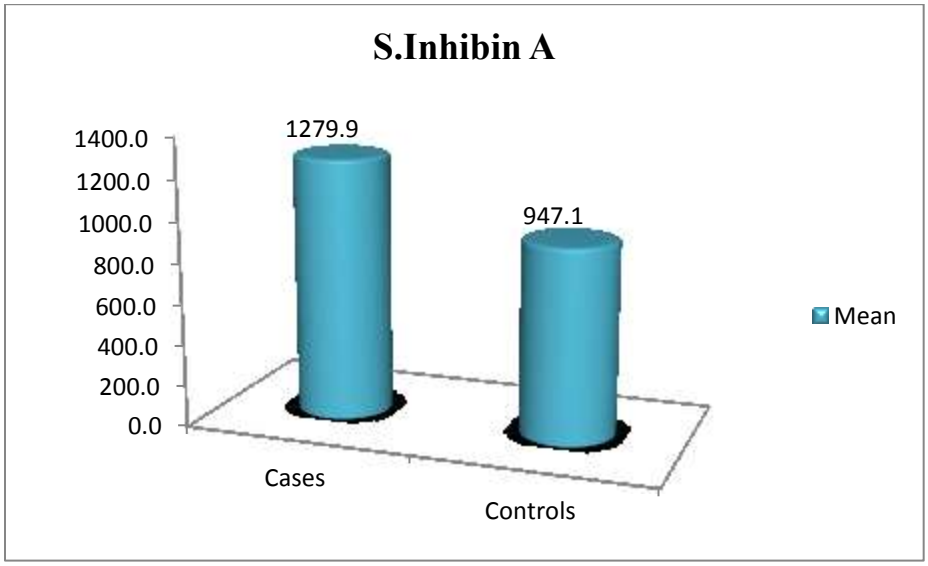

Chart 3: Bar diagram depicting the mean S.inhibin A value of the study groups

Table 4: Mean, Median and Quartiles of S.inhibin A between controls, mild preeclampsia and severe preeclampsia

	N	Mean(pg/ml)	Std. Deviation	Median(pg/ml)	25th Quartile	50th Quartile	75th Quartile
Mild	24	1053.5546	217.7749	1129.35	774.6325	1129.35	1248.8
Severe	26	1488.9231	73.91203	1520.2	1518.025	1520.2	1520.2
Controls	50	947.07	165.05	923.5	842.675	923.5	1100.5

The above table shows that the mean S. inhibin A value among the mild preeclampsia, severe preeclampsia and control group was 1053.55±217.77, 1488.92±73.91 and 947.07±165.05 pg/ml respectively.

The median value among the mild preeclampsia, severe preeclampsia and control group was 1129.35, 1520.2, 923.5 pg/ml respectively.

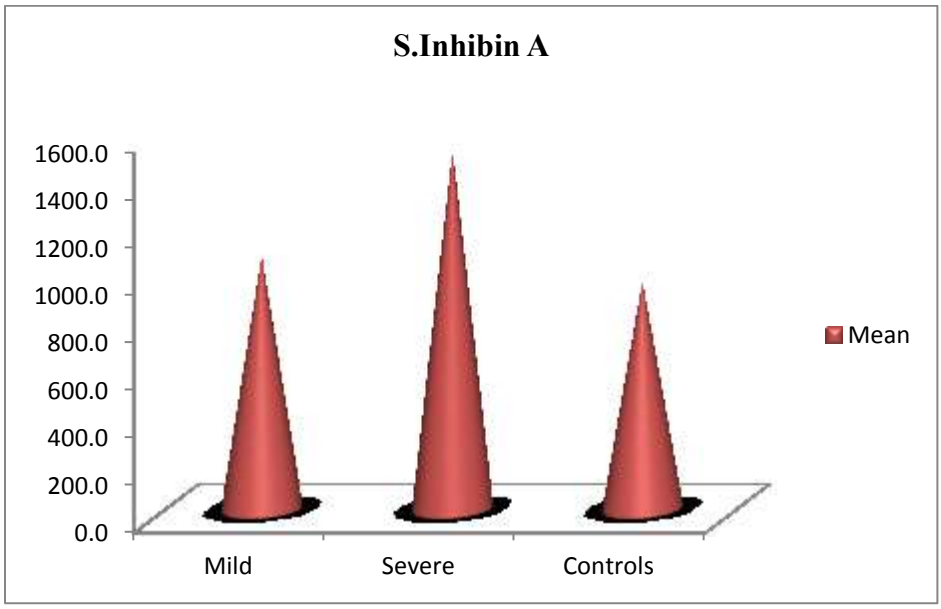

Chart 4: Bar diagram depicting the mean S. inhibin A value of the study groups (mild preeclampsia, severe preeclampsia & controls)

The p value of the mean S.inhibin A value between the mild preeclampsia & severe preeclampsia group was <0.001 suggesting that the difference was statistically highly significant.

The p value of the mean S.inhibin A value between the mild preeclampsia & control group was <0.05 suggesting that the difference was statistically significant.

The commonest mode of delivery in the preeclampsia group was LSCS (70%) followed by misoprostol induced vaginal delivery (18%) and spontaneous vaginal delivery (6%). In the normotensive group, the commonest mode of delivery was LSCS (50%) followed by spontaneous vaginal delivery (32%) and misoprostol induced vaginal delivery (12%).

In our study, between the cases and controls, term babies were 52% and 66% respectively and preterm were 28% and 34% respectively. However, 14% were IUGR and 6% fresh still born in the preeclampsia group as compared to none in the control group and these were seen more in the severe preeclampsia subgroup with higher range of S.inhibin A levels (1302 - 1520.2 pg/ml).

The maternal complication seen associated with preeclampsia in our study were eclampsia (6%), followed by abruption (4%), thrombocytopenia (4%) and pulmonary edema (2%). These were all seen in the severe preeclampsia subgroup with higher range of S.inhibin A levels (1520.2 pg/ml).

DISCUSSION: Preeclampsia is a multisystem disorder of unknown etiology with hypertension, proteinuria and/or edema, predisposing to potentially lethal complications such as eclampsia, abruption placentae, circulatory collapse, cerebral haemorrhage and hepatorenal dysfunction.
The mean **age** of this study population was 23.46±3.55 years which is comparable to the study population of Vana H et al. (25.9 years), Jaiswar SP et al.(26.03±3.99 years) and Hall et al.(26.6±5.6 years).[3,1,7] In a study by Dayal M et al. 60% of preeclampsia patients were in the age group of 20-25 yrs as seen in the present study.[8] While it was found that the mean age in the study population of Menzies et al. was 32.5 years and by Qublan et al. (28.5±3.3 years).[9,10]
The mean **gestational age** at sampling in the present study was 36.97±2.98 wks which was comparable to other studies such as Vana H et al. (36.4 wks), Menzies et al. (35.1 wks) and Phupong V et al. (36.3±3.6 wks) as per the above table.[3,9,11]
In the preeclampsia group, 52% belonged to severe preeclampsia subgroup while 48% belonged to mild preeclampsia subgroup. This was comparable to a study by Phupong V et al. where 55% belonged to severe preeclampsia and 45% mild preeclampsia subgroup.[11]

Table 5: Comparison of Inhibin A levels in different studies

STUDIES	MEAN S. Inhibin A levels		
	Normotensive	Pre Eclampsia	P value
Muttukirshna et al. 1997[12]	0.36ng/ml	3 ng/ml	<0.001
H.Laivouri et al. 1999[13]	882ng/L	1691ng/L	<0.003
Krissada et al. 2008[14]	839pg/ml	1229pg/ml	0.002
Vana et al. 2012[3]	1160pg/ml	1379pg/ml	0.255
PRESENT STUDY	947.07 pg/ml	1279.95pg/ml	<0.001**

** highly significant

It was seen that the mean **S.inhibin A levels** were greater in the preeclampsia group (1279.95 pg/ml) than in the control group (947.07 pg/ml), which was **statistically highly significant (p<0.001)**. Similar results were seen in the studies by Muttukirshna et al.[12](p<0.001), H.Laivouri et al.[13] (p<0.003) and Krissada et al.[14] (p-0.002).

Another observation in our study was the positive correlation between occurrence of severe preeclampsia and S.Inhibin A levels. The mean S.inhibin A level in severe preeclampsia was 1488.92± 73.91 pg/ml and that of mild preeclampsia was 1053.55±217.77 pg/ml, showing that the difference is **statistically highly significant (p <0.001)**. These results were comparable to several other studies. In a study conducted by Phupong V et al. the mean S. inhibin A levels in severe and mild preeclampsia were 1435.9±603.2 pg/ml vs 1021.9±438.8 pg/ml, p= 0.014).[11] Zeeman et al. and Vana et al. also showed a rise in levels of S.inhibin A with severity of preeclampsia.[16,6]

In our study though there were overlapping values between mild preeclampsia (1053.55±217.77 pg/ml) and controls (947.07±165.05 pg/ml), the difference was statistically significant ($p<0.05$). Overlapping of serum inhibin A levels in mild and severe preeclamptic patients was also observed in studies by Krissada et al., Phupong v et al., Silver et al. and Zeeman et al.[14,11,15,16] but Muttukrishna et al. reported that inhibin A levels were raised significantly in preeclampsia without overlapping of levels.[12]

CONCLUSION: The conclusion of this study is that there is a statistically **highly significant difference ($p<0.001$)** in the S.inhibin A levels between preeclampsia cases and normotensive controls and there is a rise in S.inhibin A levels with increasing severity of the disease. Hence, S.inhibin A levels can serve as an useful adjunct, though not a sole indicator, to grade the severity of the disease as early detection and management would improve maternal and neonatal outcome.

Even though there was a **significant difference ($p<0.05$)** in the mean S.inhibin A levels in mild preeclampsia and control group, there was considerable overlap in the values. Therefore, further studies maybe needed to implicate the use of S. inhibin A in detecting and predicting the development of preeclampsia, more so, its severity and associated complications.

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