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Original Research Article

Association between serum ca-125 levels and severity of pre-eclampsia: a case-control study conducted in a tertiary care centre, West Bengal

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ABSTRACT

Background: Screening test for pre-eclampsia has been a topic of extensive research in last few decades, and to identify a cost effective and accurate one is of immense importance. This study was conducted to determine an association between serum CA-125 levels and severity of pre-eclampsia, and thus to specify clinical utility of this biochemical marker in prediction, diagnosis and follow-up of pre-eclampsia.

Methods: A case-control study involving 40 women with non-severe pre-eclampsia, 40 women with severe pre-eclampsia and 40 healthy pregnant women matched for age, parity and gestational age at enrolment were taken in a tertiary care centre in West Bengal.

Results: The CA-125 levels in three categories of participants were: normotensive (15.76 ± 2.95), non-severe pre-eclampsia (26.98 ± 2.28), severe pre-eclampsia (44.99 ± 11.23), $p < 0.001$. CA-125 levels correlated positively with systolic blood pressure ($r = 0.78$, $p < 0.001$), diastolic blood pressure ($r = 0.79$, $p < 0.001$), negatively with platelet levels ($r = -0.67$, $p < 0.001$) and with birth weight of baby ($r = -0.54$, $p < 0.001$). When cut-off for serum CA-125 levels was accepted as 35 IU/ml, the sensitivity and specificity of the marker was found to be 92.1% and 97.1% respectively. Positive predictive value 95.5%, Negative predictive value 94.4%.

Conclusions: We can infer from this study that maternal serum CA-125 levels are associated with pre-eclampsia and its severity. As it is much more available and less expensive, it seems to be a promising as a screening test.

Keywords: Association, CA-125, Pre-eclampsia

INTRODUCTION

Pre-eclampsia is the leading cause of maternal and fetal mortality and morbidity worldwide, affecting 5-10% of all pregnancies.¹ It is clinically diagnosed as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on at least 2 occasions 4 hours apart and/or proteinuria > 300 mg/24 hours or in the absence of proteinuria presence of any of the following-thrombocytopenia < 1 lac/ μ l, headaches and visual disturbances, renal insufficiency (serum creatinine levels > 1.1 mg/dl), impaired liver function (blood levels of transaminases elevated twice the normal concentration), presence of pulmonary oedema. The WHO estimates that 16% of maternal deaths are due to hypertensive disorders

and over 100,00 women die from pre-eclampsia globally, with a higher incidence in developing countries (2.8%) than developed countries (0.4%).^{2,3}

It causes ischaemic end-organ damage due to diffuse endothelial dysfunction affecting eye, brain, kidney and placenta. The most accepted theory of pathogenesis is defective trophoblastic invasion of placenta into maternal decidua, causing chronic inflammation and altered vascular reactivity.⁴ Resultant maternal adaptation to this abnormal immunologic tolerance of pregnancy is immune response against placenta and even paternal antigens on fetus resulting in placental hypoxia and secreting inflammatory mediators acting on endothelium. One such mediator is CA-125.⁵

CA-125 is a glycoprotein antigen expressed from foetal chorion, amniotic fluid and maternal decidua during the 1st trimester and postpartum period, returning to normal levels during 2nd and 3rd trimester. It is a valuable marker for several benign and non-gynaecological conditions also. It is cheap, easily accessible- hence can provide a wide range of clinical use, while biomarkers like sFlt-1, PIGF, PAPP (evaluated in 1st half of pregnancy and 3rd trimester) are costly and not much in vogue.^{6,7} However, the use of CA-125 in obstetrics is experimental and under extensive research which requires multicentric studies.⁸

METHODS

This study was approved by the Institutional Review Board and Ethics Committee of Bankura Sammilani Medical College where the study was conducted in the Department of Obstetrics and Gynaecology and Department of Biochemistry from May 2019 to December 2019. Written informed consent was obtained from all participants.

The study groups included 40 healthy pregnant women, 40 women with non-severe pre-eclampsia and 40 women with severe pre-eclampsia. They were matched for age, parity and gestational age at enrolment. Our study comprised of pregnant females who visited our hospital from 28-40 weeks of gestation. The healthy pregnant women were recruited at routine antenatal care and were excluded if any complication developed later. All participants were followed up till delivery with records of maternal and neonatal outcome.

Pre-eclampsia was diagnosed and classified according to the ACOG guidelines. Pre-eclampsia was divided into non-severe and severe categories. Non-severe pre-eclampsia was defined as SBP \geq 140 mmHg and/or DBP \geq 90 mmHg on at least 2 occasions 4 hours apart and presence of proteinuria $>$ 300 mg/24 hours. Severe pre-eclampsia was defined as SBP \geq 160 mmHg and/or DBP \geq 110 mmHg and presence of any of the following-

proteinuria $>$ 5 gm/24 hours, headaches and visual disturbances, pulmonary oedema, upper abdominal pain, increased levels of transaminases twice the basal levels, serum creatinine $>$ 1.1 mg/dl, oliguria, thrombocytopenia $<$ 1 lac/ μ l or foetal growth restriction.

Patients with diabetes mellitus type II, renal disease, obesity (BMI $>$ 30), peripheral vascular disease, liver cirrhosis, multiple gestations and symptomatic infectious diseases were excluded. All patients underwent pelvic USG to rule out any ovarian tumours, endometriosis or uterine fibroids in pregnancy.

In our study, venous samples were collected when the patients presented for the first time for evaluation and before initiation of any treatment. Serum CA-125 levels were estimated with the standard ELISA technique. 24-hour urine samples were collected from each participant to determine protein excretion.

Statistical analysis

The collected data were analyzed by Statistical Package for Social Sciences (SPSS version 20). Data were expressed as mean \pm standard deviation or percentages where appropriate. Parametric variables of two groups were compared by independent samples t test, while one-way ANOVA was used to compare the parametric variables of three groups. The possible relationship between a particular biochemical parameter and stage or grade was evaluated by Pearson correlation test. Predictive power of CA-125 for preeclamptic pregnancies was determined by Chi-square test and the selectivity of this biochemical parameter was demonstrated. All significances were reported at $p < 0.05$.

RESULTS

Table 1 compares the clinical characteristics of the three study groups.

Table 1: Clinical and demographic characteristics of participants (n=120) (Mean \pm SD).

	Normotensive	Non severe preeclampsia	Severe pre eclampsia	P value
Ca125	15.76 \pm 2.96	26.97 \pm 2.28	44.99 \pm 11.27	0.001
Systolic blood pressure	122 \pm 9	148 \pm 5	168 \pm 9	0.001
Diastolic blood pressure	78 \pm 7	96 \pm 5	112 \pm 5	0.001
platelet	1.92 \pm 0.18	1.74 \pm 0.06	1.58 \pm 0.07	0.001
Birth weight	2.78 \pm 0.27	2.47 \pm 0.14	2.20 \pm 0.28	0.001
parity	1.93 \pm 0.69	1.28 \pm 0.45	1.23 \pm 0.42	0.001
Urine protein 24 hours	0.18 \pm 0.06	1.71 \pm 0.47	5.9 \pm 1.13	0.001

* $p < 0.05$ is accepted to be statistically significant

The CA-125 levels in three categories of participants were: normotensive (15.76 \pm 2.95), non-severe pre-eclampsia (26.98 \pm 2.28), severe pre-eclampsia (44.99 \pm 11.23), $p < 0.001$.

Table 2 shows significant positive correlations between maternal serum CA125 and the various clinical and laboratory markers of disease severity.

Table 2: Correlation between CA125 and markers of severity for preeclampsia.

Parameters	Pearson's co-efficient of correlation (r)	P value
Systolic blood pressure (mmHg)	0.788	0.001
Diastolic blood pressure (mmHg)	0.793	0.001
24 hours urinary protein	0.831	0.001
Platelet	-0.671	0.001
Birth weight	-0.542	0.001

*p<0.05 is accepted to be statistically significant

Table 3 shows association between CA125 and preeclampsia.

Table 3: Association between CA125 and preeclampsia.

Parameters	Normotensive	preeclampsia	Total
CA125 value <35 IU/ml	36	29	65
CA125 value ≥35 IU/ml	4	51	55
Total	40	80	120

Chi square value= 31.03, p=0.001*, *p<0.05 is accepted to be statistically significant

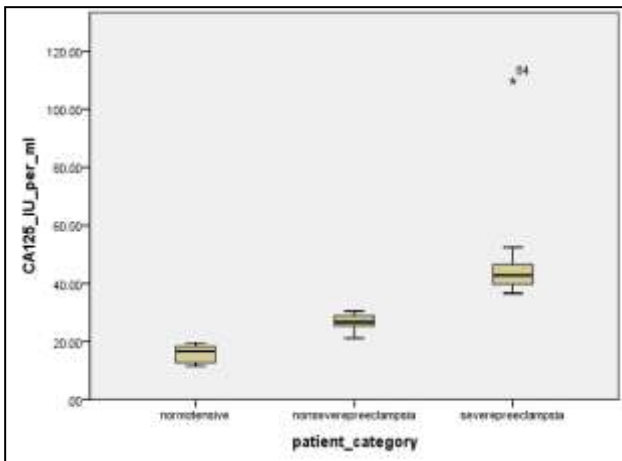


Figure 1: The distribution of CA-125 values within the control group and patients with non severe and severe preeclampsia.

Figure 1 shows the distribution of CA-125 values within the control group and patients with non severe and severe preeclampsia. Women diagnosed with severe preeclampsia had significantly less parity and platelet counts whereas their systolic and diastolic blood pressure values as well as serum concentrations of uric acid and CA-125 were significantly higher. CA-125 levels correlated positively with systolic blood pressure (r=0.78, p<0.001) (Figure 2), diastolic blood pressure (r=0.79, p<0.001) (Figure 3), negatively with platelet levels

(r=-0.67, p<0.001) (Figure 4) and with birth weight of baby (r=-0.54, p<0.001) (Figure 5). When cut-off for serum CA-125 levels was accepted as 35 IU/ml, the sensitivity and specificity of the marker was found to be 92.1% and 97.1% respectively. Positive predictive value 95.5%, negative predictive value 94.4%.

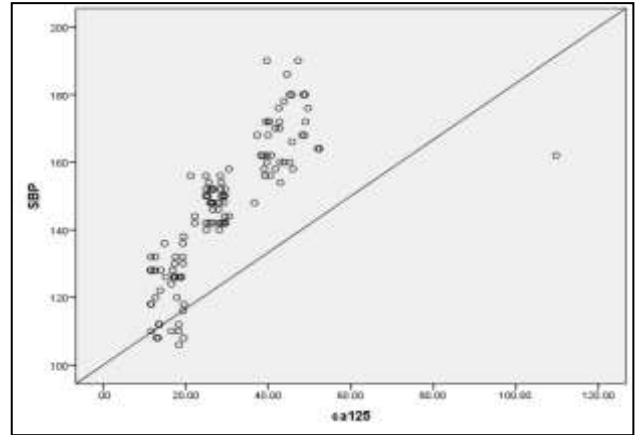


Figure 2: CA-125 levels correlated positively with systolic blood pressure (r= 0.78, p<0.001).

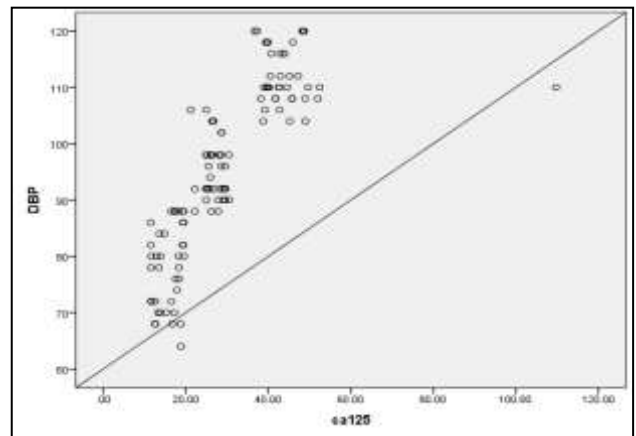


Figure 3: CA-125 levels correlated positively with diastolic blood pressure (r=0.79, p<0.001).

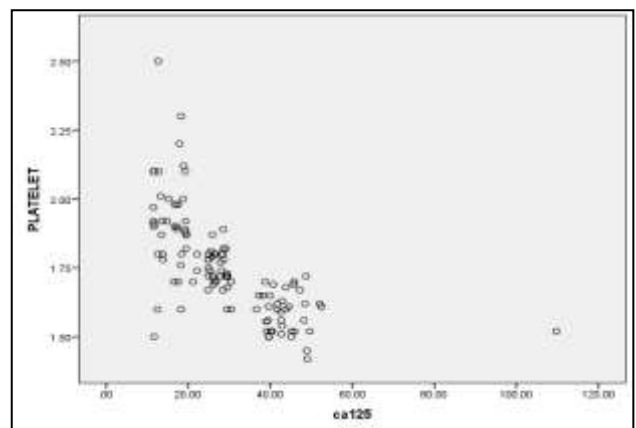


Figure 4: CA-125 levels correlated, negatively with platelet levels (r=-0.67, p<0.001).

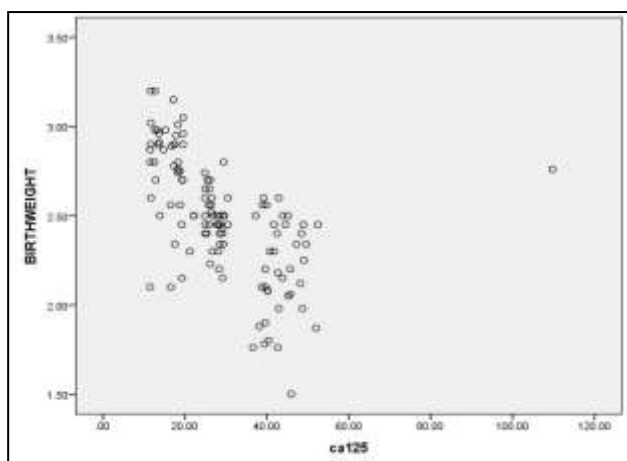


Figure 5: CA-125 levels correlated negatively with birth weight ($r=-0.54$, $p<0.001$).

DISCUSSION

Several studies have examined the association between maternal serum CA 125 levels and preeclampsia, but these studies are widely unappreciated and less data regarding this are available in Indian population. Our study shows an elevated serum CA125 levels in preeclamptic pregnancy as compared with normotensive pregnancy and an even significantly higher levels in cases of severe preeclampsia, in similar fashion to the observations in previous studies by Karaman et al and Ozat et al.^{4,5} Present study also corroborates with Cebesoy et al who found a significantly higher serum concentrations of CA125 in women with preeclampsia.⁹ Cebesoy et al proposed that the elevation of CA125 in preeclampsia is probably due to ascites found in preeclamptic women arising from hypoalbuminemia, a theory also agreed by Karaman et al, Ozat et al on the other hand proposed the failure of trophoblastic invasion with the induction of an inflammatory process within the placenta leads to the expression of CA125 in preeclampsia.^{4,5,9}

However, there occurs contradiction with some older studies. Schröcksnadel et al were the first to study the relationship between the plasma levels of CA125 in patients with hypertensive disorders of pregnancy, healthy pregnant and healthy non-pregnant controls but found no statistically significant differences in the three groups.⁶ Bon et al found that though maternal serum levels of CA125 were higher during the first and third trimesters of pregnancy, it showed no relationship with preeclampsia.⁷ De Groot et al in their study, examined CA125 levels of pregnant women (both normotensives and those who developed preeclampsia subsequently) over a time interval.⁸ They reported that CA125 did not differ with respect to their pregnancy outcome or gestational age but proposed a possible trend toward an elevation in CA125 concentrations for pregnancies that are certain to develop preeclampsia.

We have found that females diagnosed with preeclampsia have significant association with increase in systolic blood pressure, increase in diastolic blood pressure, 24 hours urinary protein levels. It has been deciphered from this study that increase in the severity of pre-eclampsia has negative association with maternal platelet levels and birth weight of the baby, and these are similar to the reports from other studies.^{4,5} Our findings thus emphasize the potential role of CA125 as biomarker or prognostic indicator of disease severity.

The limitation of this study was that it was institutional-based, and thus the findings may not be representative of the general population.

CONCLUSION

We can determine from this study that increased maternal serum CA 125 levels is associated with the incidence of preeclampsia and it may play a role in determining the severity of disease. We, therefore, recommend that further validation of these findings with more robust longitudinal studies with maternal serum CA125 profiles in pregnancy to determine its suitability as a predictive biomarker for preeclampsia as well as to determine an acceptable cut-off value particularly amongst Indian women who have a propensity to present with severe disease and adverse pregnancy outcome.

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