International Journal of Gynaecology Sciences
Online ISSN: 2664-8407, Print ISSN: 2664-8393
Received: 05-10-2019; Accepted: 06-11-2019; Published: 13-11-2019
www.gynaecologyjournal.net
Volume 1; Issue 1; 2019; Page No. 17-21

Can we use ca-125 as a biomarker for prediction of occurrence of severe pre-eclampsia in the third trimester of pregnancy?

Ahmed Alanwar[1*], Walid Abdelhady[2]
[1] Department of Obstetrics and Gynecology, Ain Shams Maternity Hospital, Faculty of Medicine, Ain Shams University, Cairo, Egypt
[2] Department of Clinical Pathology, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Abstract
Objective: The current study aims to assess the accuracy of CA-125 as a biomarker for prediction of occurrence of severe pre-eclampsia (SPE) in the third trimester of pregnancy.
Methods: An observational cohort study was conducted at Ain Shams University Maternity Hospital in Cairo, Egypt during the period between June and December 2018. This study enrolled 100 primigravida with viable, singleton fetus ≥30 week's gestation with no other obstetric or medical co-morbidities. CA-125 was drawn at enrollment. They were then followed up weekly and on termination they were categorized into the study group: SPE and control group (normal). The CA-125 was drawn again on termination. The primary outcome of the study was the rate of elevated maternal CA-125 in women diagnosed with SPE.
Results: CA-125 levels were significantly higher both at enrollment and termination in the SPE group compared to the control group (p <.001). Similarly, the change in CA-125 levels was significantly higher in the SPE group compared to the control group (p <.001). Statistically significant positive correlation was found between CA-125 levels with systolic and diastolic blood pressure values (p <.001). Moreover, a statistically significant negative correlation was found between CA-125 levels with platelet count and gestational age at time of termination. CA-125 level at termination had the highest sensitivity and specificity for prediction of SPE with a cutoff of 41 U/mL.
Conclusions: CA-125 could be used as a valuable potential biomarker for prediction of SPE in third trimester of pregnancy.

Keywords: pre-eclampsia, CA-125, maternal morbidity, pregnancy

Introduction

Hypertensive disorders of pregnancy (HDPs) occur in nearly 7-10% of all pregnancies. Amongst them, pre-eclampsia (PE) is a major cause of high-risk pregnancies. PE is characterized by hypertension and arteriolar vasoconstriction, which decrease the uteroplacental perfusion and ultimately result in placental hypoxia which if long lasts can impair fetal growth [1]. PE is diagnosed after the 20th week of pregnancy in previously normotensive women. Its clinical features include hypertension (blood pressure > 140/90 mmHg), proteinuria (24 hours total urinary protein > 300 mg/24 h), and varying degrees of ischemic end-organ damage, which are thought to result from diffuse endothelial dysfunction [2].

The exact pathophysiology of PE is unknown; however, the mechanism may be due to abnormal trophoblastic invasion of uterine vessels, abnormal nitric oxide and lipid metabolism, immunologic intolerance between fetoplacental and maternal tissue, genetic abnormalities, inadaptability to inflammation and cardiovascular changes, and metabolic and nutritional factors [3]. A great deal of effort has been directed at the identification of demographic factors, biochemical analytes, or biophysical findings, alone or in combination, to predict early in pregnancy the later development of PE. Although there are some encouraging findings, these tests are not yet ready for clinical use [4].

Cancer Antigen-125 (CA-125) is a glycoprotein antigen, which is generally expressed in epithelial ovarian cancer and non-malignant pelvic diseases like endometriosis, fibroids, pregnancy, and pelvic inflammatory disease [5]. Fetal chorion, amniotic fluid and maternal decidua are potential sources of high serum CA-125 levels during the first gestational trimester and the postpartum period. The role of CA-125 levels within the perinatal period is still under study [6]. The clinical studies related to the use of CA-125 in HDPs are few and report conflicting results [2, 7].

It is assumed that PE is related to decrease trophoblastic migration into the maternal decidua, which leads to chronic inflammation within the placenta. This process may lead to increased expression of CA-125. The underlying inflammatory process worsens when PE becomes severe in a patient. Thus, it can be hypothesized that maternal serum CA-125 levels will be higher in pregnant women with severe pre-eclampsia (SPE) than in other patients. It may be assumed that the extension of decidual destruction and failure of trophoblastic invasion in PE may induce the secretion of CA-125 within placenta [8]. Attention has therefore turned in recent years towards identifying maternal markers of placental dysfunction which are raised in women who go on to develop PE [9].

The present study aims to assess the accuracy of CA-125 as a biomarker for prediction of SPE in the third trimester of pregnancy.

Materials and Methods

This was a pilot observational cohort study conducted at a

tertiary University Hospital during the period between June and December 2018. A total of 198 primigravida women ≥ 30 weeks gestation were initially assessed for eligibility to be recruited into the study. Ninety-eight women were excluded from the study. Exclusion criteria were women with multiple pregnancies, gestational hypertension, PE or other medical co-morbidities such as diabetes mellitus, SLE, thyroid disorders or other obstetric complications.

One hundred primigravida with singleton pregnancies were enrolled in the study. The Institutional review and ethical board approval were obtained, and all participants provided informed written consent following a discussion on the nature of the study.

Women were subjected to history taking, clinical examination included body mass index (BMI) assessment and blood pressure (BP) measurement, ultrasound examination (to exclude ovarian pathology) and investigations drawn (complete blood count, liver enzymes; AST and ALT, kidney functions; Serum creatinine, urine dipstick analysis of Albumin). After fulfilling the inclusion and exclusion criteria, CA-125 was drawn at enrollment.

Then, patients were followed up weekly in the antenatal care clinic with recording of BP and urine dipstick analysis in each visit. At termination of pregnancy, they were categorized into the study group (SPE) and the control group (normal pregnancies). The CA-125 was drawn again immediately after delivery whatever vaginally or by cesarean section. Serum levels of CA-125 were measured by electro-chemiluminescence immunoassay (Roche Elecsys Kits, Roche Diagnostics, Mannheim, Germany).

Outcomes

Primary Outcome

Elevated maternal CA-125 in women diagnosed with SPE.

Secondary Outcomes

Correlation between CA-125 and systolic blood pressure.
Correlation between CA-125 and diastolic blood pressure.
Correlation between CA-125 and platelet count.
Correlation between CA-125 and gestational age at birth.

Sample size calculation:

Depending on Karaman, *et al*. who found that CA-125 level 38.5±20.9 in severe preeclampsia, 17.2±8.2 in apparently healthy pregnant [8], we adjusted the power= 0.99 and α=0.05, and by using PASS 11th release the minimal sample size for an equal size case control study to detect a significant statistical difference between severe and healthy individuals is 50 cases.

Statistical Analysis

Data collected, tabulated, coded and analyzed by computer software SPSS (Statistical program for social science) version 22.0. Numerical variables were examined for normality then, expressed as mean (standard deviation) or the median whenever possible. On the other hand, Categorical variables were presented as number of cases (percentage). Between groups, comparison of numerical variables was performed by Student's test if they show normal distribution; Otherwise, Mann Whitney test was used instead. Between groups, comparison of categorical variables was performed by Chi-square test.

Pearson correlation analysis was used between CA-125 and BP, gestational age at termination and platelet count. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of CA-125 were calculated for prediction of SPE. P-value <0.05 was considered statistically significant.

Results

Twelve women were excluded during the trial; four had eclamptic fits at delivery, two women had developed placental abruption and six women were lost during follow up. At the end of the trial the SPE group comprised 14 women and the control group 74 women.

No significant differences were found between both groups regarding age (p=.06). However, women of the SPE group tended to have significantly higher BMI and lower gestational age at termination compared to the control group (p<.001).

Hemoglobin concentration was statistically significant higher in the SPE group compared to the control group (P=.002), this slight difference might reflect the hemoconcentration observed in SPE patients. Platelet counts were significantly lower, and albuminuria was significantly higher in the SPE group compared to the control group. No significant differences were found between women of both groups regarding ALT, AST and serum creatinine levels as patient with HELLP syndrome and other complications of PE were excluded from our study [Table 1].

CA-125 levels were significantly higher both at enrollment and termination in the SPE group compared to the control group (P<.001). Additionally, the change in CA-125 levels was significantly higher in the SPE group compared to the control group (P<.001) [Table 2].

There was a statistically significant positive correlation between CA-125 levels (at enrollment, termination and the magnitude of change) with systolic and diastolic blood pressure values (p<.001). Also, a statistically significant negative correlation was found between CA-125 levels with platelet count and gestational age at time of termination [Table 3, Figure 1].

On ROC analysis of CA-125 levels in prediction of SPE, the diagnostic performance of CA-125 levels in prediction of SPE is shown in table 4. CA-125 level at termination had the highest sensitivity and specificity for prediction of SPE with a cutoff of 41 U/mL [Table 4, Figure 2].

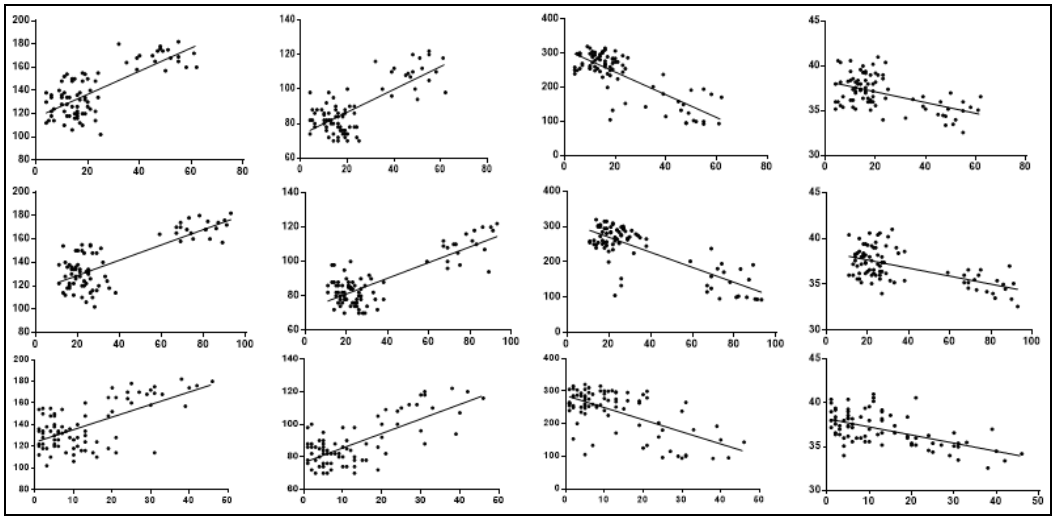

Fig 1: Scatter diagrams summarizing correlation between CA-125 levels at enrollment (upper row), termination (middle row) and change in its level (lower row) with systolic blood pressure, diastolic blood pressure, platelet counts and gestational age at termination (from left to right in order respectively)

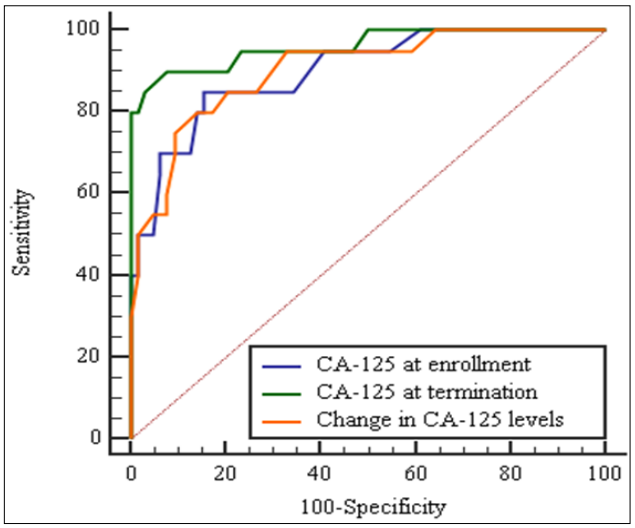

Fig 2: ROC curve for prediction of severe preeclampsia using CA-125 levels.

Table 1: Comparison between the two groups regarding demographic, clinical characteristics and laboratory findings. * Statistical significant difference SPE; severe pre-eclampsia, BMI; body mass index, Hb; hemoglobin, ALT; alanine transaminase. AST; aspartate transaminase, IQR; inter-quartile range

	SPE group (n=14)	**Control group (n=74)**	**P-value**
Age (Yrs)			
Range	18.0 – 34.0	19.0 – 38.0	0.06
Mean±SD	24.15 ± 4.27	26.26 ± 4.39	
BMI (Kg/m^2)			
Range	25.3 – 39.3	19.0 – 33.3	<0.001*
Mean ± SD	30.83 ± 3.60	24.18 ± 3.38	
Gestational age at termination (wks)			
Range	32.0 – 37.0	34.0 – 41.0	<0.001*
Mean ± SD	35.05 ± 1.17	37.59 ± 1.63	
Systolic blood pressure (mmHg)			
Range	157.0 – 182.0	102.0 – 155.0	<0.001*
Mean±SD	169.25 ± 7.26	129.56 ± 13.55	
Diastolic blood pressure (mmHg)			
Range	94.0 – 122.0	70.0 – 100.0	<0.001*
Mean±SD	109.25 ± 8.39	81.64 ± 7.18	
Hb (gm/dL)			
Range	11.00 – 13.20	9.10 – 12.00	0.002*
Mean±SD	12.04 ± 0.68	10.46 ± 0.88	
Platelets (×10^3/mm^3)			
Range	93.00 – 238.00	105.00 – 320.00	<0.001*
Mean ± SD	143.25 ± 44.38	267.23 ± 39.56	
ALT (U/L)			

Range	10.00 – 48.00	10.00 – 48.0	0.86
Mean±SD	29.00 ± 11.83	29.50 ± 11.67	
AST (U/L)			
Range	12.00 – 50.00	12.00 – 50.00	0.75
Mean±SD	31.00 ± 11.83	30.09 ± 11.40	
Serum creatinine (mg/dL)			
Range	0.50 – 0.90	0.50 – 0.90	0.90
Mean±SD	0.64 ± 0.11	0.64 ± 0.11	
Albuminuria			
Range	1.0 – 3.0	0.0 – 1.0	<0.001*
Median (IQR)	2 (1 – 2)	0 (0 – 0)	

Table 2: Comparison between the two groups regarding CA-125 levels.

	SPE group (n=14)	Control group (n=74)	P-value
CA-125 at enrollment			
Range	32.0 – 62.0	4.0 – 25.0	<0.001*
Mean±SD	48.35 ± 8.28	14.18 ± 5.61	
CA-125 at termination			
Range	59.0 – 93.0	11.0 – 38.0	<0.001*
Mean ± SD	77.70 ± 9.69	22.17 ± 6.45	
Change in CA-125 level			
Range	13.0 – 46.0	1.0 – 31.0	<0.001*
Mean±SD	29.35 ± 8.49	7.98 ± 6.18	

* Statistical significant difference SPE; severe pre-eclampsia,

Table 3: Correlation between CA-125 levels, blood pressure, platelet count and gestational age at termination of the study population.

	CA-125 at enrollment		CA-125 at termination		Change in CA-125 levels	
	r	p	r	p	r	p
Systolic blood pressure	0.58	<0.001*	0.51	<0.001*	0.43	<0.001*
Diastolic blood pressure	0.41	<0.001*	0.43	<0.001*	0.50	<0.001*
Platelet count	- 0.62	<0.001*	- 0.5	<0.001*	- 0.43	<0.001*
Gestational age at termination	- 0.36	0.003*	- 0.45	<0.001*	- 0.49	<0.001*

* Statistical significant difference

Table 4: Receiver-operating characteristic (ROC) curve analysis for prediction of severe preeclampsia using CA-125 levels.

Predictor				
Variable		CA-125 at enrolment	CA-125 at termination	Change in CA-125 level
AUROC		0.90	0.961	0.903
95% CI		0.81-0.95	0.89-0.99	0.81-0.95
p-value (AUC=0.5)		< 0.001*	< 0.001*	< 0.001*
Cut-off value		> 32	> 41	> 18.0
Validity	Sensitivity (%)	85.0%	90.0%	80.0%
	Specificity (%)	84.37%	92.19%	85.94%
	PPV (%)	63.0%	78.3%	64.5%
	NPV (%)	94.7%	96.7%	93.2%
	Positive likelihood ratio	5.44	11.52	5.69
	Negative likelihood ratio	0.18	0.11	0.23

* Statistical significant difference

AUROC; area under the curve, CI; confidence interval, PPV; positive predictive value, NPV; negative predictive value

Discussion

Pre-eclampsia is a leading cause of maternal and perinatal mortality and morbidity. The exact cause of PE is unknown however; the basic pathology is endothelial dysfunction and intense vasospasm [1]. The presentation is highly variable, but generally includes the combination of maternal hypertension and proteinuria. The etiology of the disease is likely multifactorial, and its initial presentation may be mild or severe preeclampsia, including eclampsia. Globally, PE and eclampsia account for 10-15% of maternal deaths. Most deaths in developing countries results from eclampsia [10].

This study was done to assess the accuracy of CA-125 as a biomarker for prediction of SPE in pregnant women at the third trimester. We found that CA-125 levels were significantly higher both at enrollment and termination in the SPE group compared to the control group. The mean value for the SPE group for CA-125 level at enrollment was 48.35 ± 8.28 U/mL whilst the mean value for the control group was 14.18 ± 5.61 U/mL (p <.001). In our study we found out that at termination, the CA-125 level was significantly, much higher in the SPET group, with a value of 77.70 ± 9.69 U/mL as compared to 22.17 ± 6.45 U/mL in the control group. Following on the same path, it was found that the increase in CA-125 level from enrollment to termination was also much higher with a range of 29.35 ± 8.49 U/mL and 7.98 ± 6.18 U/mL for both groups respectively.

In our study, serum CA-125 concentrations were found to correlate positively with systolic blood pressure (r =0.51, p <.001), diastolic blood pressure (r =0.43, p <.001), and negatively with platelet count (r = -0.5, p <.001), and gestational age at birth (r = 0.45, p <0.001)**.** When the cut-off point for serum CA-125 concentrations was accepted as 41 U/mL, the sensitivity, specificity, positive and negative predictive values of this biochemical marker were 90.0%, 92.19%, 78.3% and 96.7% respectively for the detection of SPE pregnancies.

A few clinical studies have investigated whether this enhancement in CA-125 expression would become biochemically and clinically evident or not. In contrast to this study, Schrocksnadel *et al*. compared the plasma CA-125 levels of 50 healthy non-pregnant women, 50 pregnant patients with hypertensive disorders and 50 healthy women with singleton pregnancies at term. No statistically significant difference could be noted for CA- 125 levels. This study, which compared CA-125 values of healthy and PE subjects throughout a given time interval, documented that serum concentrations of CA-125 did not differ with respect to either pregnancy outcome or gestational age. There was a trend toward an elevation in CA-125 concentrations for pregnancies that are destined to develop PE [12].

Bon *et al*, compared serum CA-125 concentrations of 120 women with pathological outcome of pregnancy (spontaneous abortion, fetal death, intrauterine growth retardation, chromosomal and structural abnormalities, and PE/ eclampsia) to women with normal outcome of pregnancy. It was reported that maternal CA-125 serum values were not significantly different from those values obtained in pathological pregnancies as compared to normal pregnancies. These results are not consistent with our study [13].

In accordance with this study, a cross sectional study conducted by Cebesoy *et al*, in which they investigated 54

Preeclamptic/eclamptic women and 56 healthy pregnant women. The serum concentrations of CRP and CA-125 were found to be significantly higher in women with PE/ eclampsia when compared with healthy pregnant women. Also, significant correlations were found between CRP, albumin, CA-125 and mean arterial pressure. Therefore, the authors concluded that CRP and CA- 125 are elevating markers in PE [2].

Similarly, Bhattacharya *et al*. report that CA-125 correlates directly with all of the biochemical markers which are commonly used to diagnose and follow women with PE. A significant but inverse relationship is also observed between the serum concentrations of CA-125 and perinatal outcome of preeclamptic women. The study suggests that CA-125 is a biochemical marker which reflects the severity of the underlying inflammatory process in PE (with a cut-off point of 50 U/mL). It may be assumed that the extension of decidual destruction and failure of trophoblastic invasion in preeclampsia may induce the secretion of CA-125 within placenta [14].

The discrepancies between the present findings and the results of the previously published studies may be attributed to several factors including the size of the study sample, the differences within the demographic and clinical features of the reviewed patients and the utilization of different diagnostic criteria for hypertensive disorders of pregnancy.

Another confounding factor may be the variance in the accuracy and reliability of CA-125 assays. A study by Lehnen *et al*. mention an automated method for the determination of the soluble fms-like tyrosine kinase (sFlt-1)/placental growth factor (PIGF) ratio in the assessment of PE and in the differential diagnosis of patients with atypical presentations of PE, these are not suited for simple, low-cost, and rapid routine clinical screenings due to financial and practical concerns. Since CA-125 is a much more available and relatively less expensive test, it seems to be a promising biochemical marker for screening PE [15].

Further research is needed to explain the exact pathogenesis of elevated serum concentrations of CA-125 in women with PE and to clarify the clinical utility of CA-125 in PE. A point of weakness in this study is that the sample size is small, and further studies with bigger sample sizes can be done to help show the higher effectiveness of CA-125 as a screening method for SPE. In addition, studies in the future could investigate at an earlier gestational age rather than 30weeks as we did in this study.

In conclusion, CA-125 could be used a valuable potential biomarker for prediction of SPE in the third trimester of pregnancy.

Conflict of interest

The authors declare that they have no conflict of interest.

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