Serum Concentration of Cancer Antigen 125 in Normal and Preeclamptic Pregnancies

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Abstract

Aim: To measure the serum concentration of CA125 in pregnancies complicated by preeclampsia and low risk pregnancies with the possibility it being considered to be used in early diagnosis of severe preeclampsia so, it may be a marker of the severity of the disease.

Methods: One hundred and eighty-nine pregnant women were participated in the study, it was carried out at department of obstetrics and gynecology, Suez Canal University Hospitals. They were divided into 3 groups mild, severe preeclampsia and normal study group. Urine analysis, complete blood count (CBC), serum AST and ALT, uric acid, urea, creatinine and serum CA125 were assayed for all participants.

Results: The mean serum concentration of CA-125 was (32.59 ± 1.63), (39.70± 1.19) and (52.92 ± 2.88) in control, mild and severe preeclampsia respectively, the difference was statistically significant (p=0.001).It wasfoundthatCA125positivelycorrelatedwithsystolic blood pressure, diastolic bloodpressure, proteinuria, hemoglobin level,ALT, AST, serum uric acid,serum creatinineand urea,meanwhile, the plateletcountshowed negative correlation withCA125(p<0.05).Receiver operating characteristics (ROC) curve was used to find out the best cut off value of CA 125 in mild and sever preeclampsia, it was 39 in mild preeclampsiawith sensitivity of 80.9%, specificity 99 %, PPV 99.4% and NPV 84%.The best cut off value was 49.5 in severe preeclampsia, the sensitivity, specificity, PPV and NPV were 82.5 %, 99 %, 99 % and 87.2 respectively.

Conclusion: SerumCA-125leveliselevatedsignificantly inmild and severepreeclampsia,itcorrelated with the severity of preeclampsia,soserum concentration ofCA125 maybeusedas a marker ofsevorityof preeclampsia.

Key words: Cancer Antigen 125 Concentration, Preeclampsia
Maternal serum ferritin may be a useful test in the prediction of asymmetric IUGR.

Introduction

Preeclampsiaisasyndromespecificto pregnancythataffectsalmostevery organ[1]. Hypertensive disorders of pregnancy affect8–10% of primigravidafemalesand aretheleading causeofmaternalandfetal morbidity andmortality worldwide. Preeclampsia isa hypertensive syndrome occurring during pregnancy thatis clinically diagnosed by hypertension (bloodpressure >140/90mmHg), proteinuria(>300 mg/24 h)and varying degreesof ischemic endorgandamage, whichist-

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houghtto betheresultof abnormal trophoblastic invasion and diffuseendothelialdysfunction-likeinthebrain, eye, kidneyand also in placenta[2].

Theexactpathophysiology of preeclampsiaisunknown;however, the mechanismmay beduetoabnormal trophoblastic invasionof uterinevessels, abnormalnitric oxide and lipid metabolism, immunologicintolerancebetweenfeto-placental and maternal tissue, geneticabnormalities,inadaptability to inflammation and cardiovascularchanges, andmetabolicandnutritionalfactors[3].

Cancerantigen125(CA-125) isa highmolecular weight heterogeneously structuredglycoprotein.It hasbeenused indiagnosis;followup treatmentandrecurrence ofepithelial ovariancancer. CA-125isa valuable marker of other gynecologicalconditions including pleuralandperitoneal involvement,the sourceof CA-125during pregnancy isthefetalchorionamnioticfluid, and maternaldecidua[4].**Schrocksnadel et al (2000)** who was the first to compare the plasma CA-125 level in healthy non-pregnant women, pregnant patients with hypertensive disorders and healthy women with singleton pregnancies at term and found no significant difference(5).On the other hand,Cebesoyand Dikensoy (2009)confirmed the relationship between the cancer antigen-125 (CA-125) with preeclampsia. They stated that CA-125 level was higher significantly in severe preeclampsia(6), soon the merits of thisdebate,weaimed to measuretheserumconcentrationofCA125inpregnancies complicatedbypreeclampsiaandlowriskpregnancieswiththepossibilityitbeing consideredtobeusedinthe earlydiagnosisof severepreeclampsiaso it may be amarkeroftheseverityof the disease.

Patients and methods

A prospectivecase-controlstudywas carried out at emergency ward, obstetrics and gynecology department at Suez Canal University Hospitals, from April 2014 to April 2016. The study was approved by the ethical committee of faculty of medicine, Suez Canal University and an informed written consent was obtained from all participants. One hundred and eighty-nine pregnant women were recruited for this study, they were divided into 3 groups 63 each;mild preeclampsia group(blood pressure ≥ 140/90 mmHg and<160/110 with proteinuria, 300mg/24hr urine collection, or +1 dipstick in urine sample).Severe preeclampsia group;pregnant women had one or more of the following criteria systolic B P ≥ 160mmHg, diastolic BP ≥ 110mmHg, proteinuria≥5gm in 24hrs urine collection or +3 dipstick in urine sample, oliguria (<500ml/d), cerebral or visual disturbance, pulmonary edema, epigastric or right upper quadrant pain, impaired liver function, thrombocytopenia (<100000) or fetal growth destruction(1) and healthy pregnant women control group. Inclusion criteria were age between 18 and 35 years, primigravida, gestational age from 28 to 40 weeks and Singleton pregnancy.Exclusion criteria were history of chronic hypertension, diabetes mellitus, renal disease, cardiovascular disease or autoimmune disease.

Complete urine analysis, complete blood count, serum AST and ALT, kidney function tests (urea and creatinine) and serum CA125 were done for all participants.Venous blood samples were withdrawn and the serum was separatedwith exclusion of grossly hemolytic, lipemic and turbid samples. Specimens were stored -20oCtill measurement of serum CA-125concentration.CA125 (Human) ELISA Kits were purched for Abnova Company Taiwan (BIOTEC Alex). CA125 was measured using the ELISA method at wave length 450nm.

Statistical analysis

The data collected were tabulated & analyzed by SPSS (statistical package for the social science software) statistical package version 11 on IBM compatible computer. Quantitative data were expressed as mean& standard deviation (SD) and analyzed by ANOVA-test for comparison of three groups followed by post hoc test. Qualitative data were expressed as number and percentage (N & %) and analyzed by applying Chi-square test. **Spearman's correlation** test was done to study correlation between one qualitative variable and one quantitative variable or two quantitative variables of not normally distributed data.**Roc curve (Receiver operating characteristic curve)**: was done to detect cut level of any tested variable where at this level there is the bestsensitivity and specificity.

Result

Onehundredandeighty-nine pregnant women were enrolled in the study, 63 patients with mild preeclampsia, 63 patients with severe preeclampsia and 63 low risk controls. There was no statistically significant difference between the three studied groups as regards the mean of maternal age and parity (P>0.05), meanwhile, the mean gestational age was statisticallysignificant, it was (38.9±1.2), (38.1±1.5) and (36±2.5) in the control, mild and severe preeclampsia groups respectively with p-value < 0.001(table 1).

In the current study the mean serum concentration of CA125 was (32.59 ±1.63), (39.70± 1.19), (52.92 ± 2.88) in control mild and severe preeclampsia respectively, the difference was statistically significant (p=0.001), which indicates that serum CA125 level increase with the severity of preeclampsia. There was statistically difference between the studied groups regarding BP, HB, platelet count, uric acid, creatinine, urea, ALT, AST (p<0.05) (table 2).

Post-hoc analysis was performed for each variable the difference between control and severe preeclampsia groups was statistically significant for all variables and also, the difference between mild and severe preeclampsia groups was significant, meanwhile, the difference between control and mild preeclampsia groups was significant only for systolic and diastolic blood pressure, serum uric acid, creatinine and CA125 (P<0.05).

The relations between cancer antigen 125 (CA125) and each of: systolic blood pressure, diastolic blood pressure, proteinuria, hemoglobin level, platelet count urea and AST and ALT were assessed by spearman's correlation coefficient, all correlations were positive except for platelet count which shows negative correlation with CA 125. All correlations were statistically significant (p<0.05) (table3).

Receiver operating characteristics (ROC) curve was used to find out the best cut off value of CA 125 in mild preeclampsia, 39 was chosen as the best cutoff value (figure I) with sensitivity of 80.9%, specificity 99 %, PPV 99.4% and NPV 84%(table 4). In severe preeclampsia, the best cutoff value was 49.5(figure II), the sensitivity, specificity, PPV and NPV were 82.5 %, 99 %, 99 % and 87.2% respectively (table 5).

Table (1): Comparison of socio-demographic characteristics of the studied population

Title		Control (n=63)		Mild (n=63)		Sever (n=63)		P-Value#
		No.	%	No.	%	No.	%	
Age	17-	25	39.68	19	31.16	22	34.92	0.485
	23-	25	39.68	23	36.51	26	41.27	
	29-34	13	20.63	21	33.33	15	23.81	
		Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
		24.52	4.53	25.37	4.55	24.54	4.36	
Parity	PG	63	100.0	63	100.0	63	100.0	
Gestational Age	28 to <33	0	0.00	0	0.00	9	14.29	0.000*
	33 to <38	9	14.29	15	14.29	37	58.73	
	38-41	54	85.71	48	85.71	17	26.98	
		Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
		38.98	1.19	38.1	1.51	36.00	2.51	

ANOVA Test* statistically significant difference

Table (2): Comparison of clinical and laboratory measures between the studied groups

Title	Control (n=63)		Mild (n=63)		Severe (n=63)		P-Value#	LSD p-value
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**		
CA125	32.59	1.63	39.70	1.19	52.92	2.88	0.001*	A:0.01* B:0.00* C:0.01*
SBP	107.06	11.35	144.29	3.09	171.27	9.16	0.001*	A:0.01* B:0.00* C:0.01*
DBP	63.73	6.09	95.79	3.83	112.78	4.38	0.001*	A:0.00* B:0.00* C:0.00*
HB	10.20	1.01	10.21	1.01	10.87	0.69	0.002*	A:0.915 B:0.00* C:0.01*
PLT ($x10^3$)	268.86	59.78	278.48	65.35	212.44	51.51	0.001*	A:0.363 B:0.00* C:0.01*
Serum uric acid	2.93	0.30	4.53	0.28	5.67	0.67	0.000*	A:0.02* B:0.00* C:0.01*
Serum Creatinine	0.58	0.10	0.77	0.15	0.93	0.15	0.001*	A:0.01* B:0.00* C:0.01*
Serum Urea	33.27	2.74	33.27	2.74	35.13	4.15	0.014*	A:1.00 B:0.00* C:0.00*
AST	26.32	4.49	26.32	4.49	39.38	5.30	0.001*	A:1.00 B:0.00* C:0.00*
ALT	27.16	4.21	27.16	4.21	38.78	5.34	0.002*	A:1.00 B:0.00* C:0.00*

SBP: systolic blood pressureDBP: diastolic blood pressure.
Kruskal Wallis Test * statistically significant at 95% level of confidence.
(LSD) least significant difference was determined:A: between control and mild.
B: between control and severeC: between mild and severe.

Table (3): Spearman's correlation coefficient (r) between CA 125, blood pressure and laboratory investigations.

	CA 125	
	R	**p-value**
Systolic blood pressure	0.903	0.000*
Diastolic blood pressure	0.908	0.000*
Proteinuria	0.936	0.001*
Hemoglobin level	0.235	0.001*
Platelet count	-0.364	0.002*
Uric acid	0.888	0.000*
AST	0.620	0.001*
ALT	0.614	0.001*
Creatinine	0.675	0.002*
Urea	0.174	0.017*

*Statistically significant at 95% level of confidence.

Table (4): Best cut-off value of CA 125 in mild preeclampsia from controls

	Mild preeclampsia No (%)	**Control No (%)**
≥ 39	51	0
< 39	12	63
Sensitivity	80.9%	
Specificity	99 %	
PPV	99.4%	
NPV	84%	
Area under the curve	0.905(0.845-0.964)	
p-value	0.001*	

PPV: positive predictive valueNPV: negative predictive value
*Statistically significant at 95% level of confidence.

Table (5): CA 125 best cutoff value in severe preeclampsia.

	Severe Preeclampsia No (%)	**Control and mild preeclampsia No (%)**
≥ 49.5	52	0
< 49.5	11	75
Sensitivity	82.5 %	
Specificity	99 %	
PPV	99 %	
NPV	87.2 %	
Area under the curve	0.965(0.94-0.989)	
p-value	0.000*	

PPV: positive predictive value.NPV: negative predictive value.
*Statistically significant at 95% level of confidence.

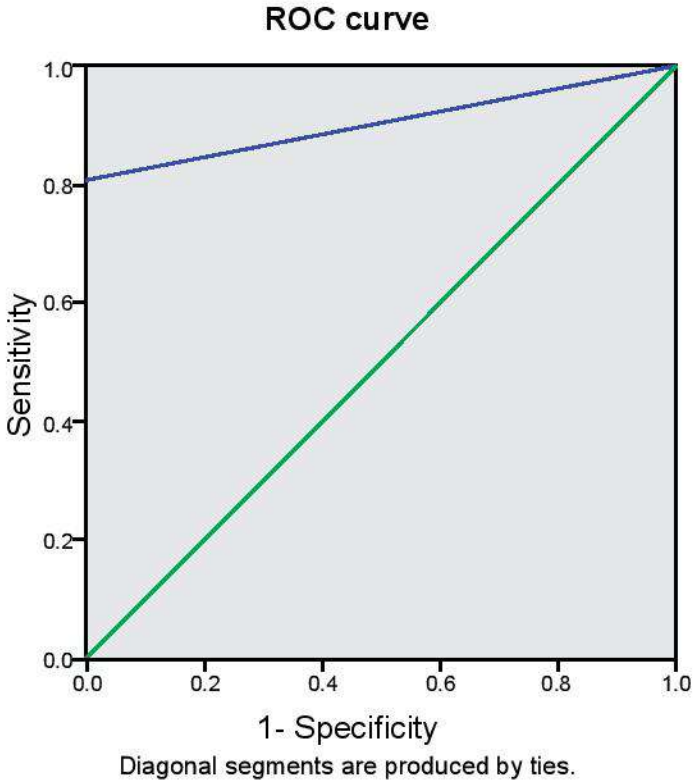

Fig (I): ROC curve for CA 125 values in mild preeclampsia.

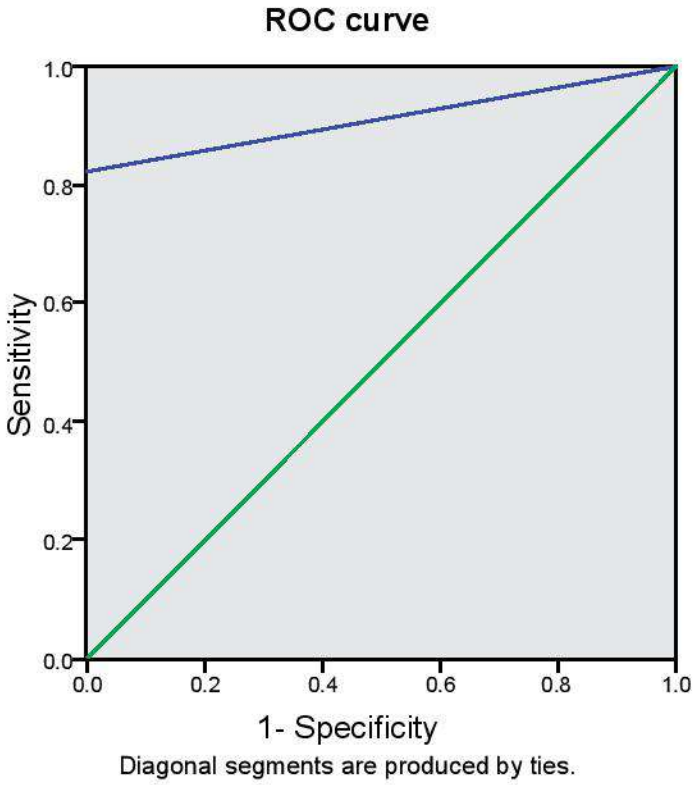

Fig (II): ROC curve for CA 125 cut off values in severe preeclampsia.

Dissussion

Preeclampsia is a hypertensive disorder of pregnancy which may cause morbidity and even mortality for both the mother and the fetus. Blood pressure elevation is the most visible sign of preeclampsia, but this disease may cause generalized damage to the maternal endothelium,kidneys and liver through the release of vasoconstrictive substances[4].CA-125 is a glycoprotein antigen which is located on cell surface; it is a molecule of 200-kDa glycoprotein initially identified on the surface of the OVCA433 ovarian carcinoma cell line[7]. CA-125 is widely distributed on the surface of both healthy and malignant cells of mesothelial origin, including pleural, pericardial, peritoneal, and endometrial cells, as well as in the normal genital tract and amniotic membrane. Fetal chorion and maternal decidua have been indicated as the potential sources of high serum CA-125 levels which are detected during the first trimester of pregnancy and postpartum period [8].

In the present study, the demographic data of the patients enrolled in the study, there were no statistically significant difference between the three studied groups control, mild and severe preeclamptic groups regarding the maternal age but there were statistically significant difference between them regarding the mean of gestational age, these findings were confirmed by **Danisman and Rousso(2011)**[9] who studied CA125 concentration in 242 patients with singleton pregnancies and primigravida divided into three groups control, mild and severe preeclampsia and found no statistically significant differences between the mean maternal age groups, while statistically significant differences between them regarding gestational age due to preterm delivery of the fetuses with preeclampsia with increasing severity of the disease.

In the current study the **mean serum** concentration of CA125 was (32.59 ± 1.63), (39.70± 1.19), (52.92 ± 2.88) in control mild and severe preeclampsia respectively which indicates that serum CA125 level increase with the severity of preeclampsia. This may be explained as serum CA125 level related to impaired placentation which causes intermittent disruption of placental perfusion, ischemia-reperfusion type injury, oxidative stress and systemic inflammatory response.This was in agreement with **Karamanand Ark (2013)** [10],

who studied 93 patients who were primigravida, they found that the mean serum concentration of CA125 in control group was (34.25 ± 3.34), it was (39.70±8.72) in mild preeclampsia and (56.11± 4.28) in severe group, an underlying inflammatory process may play a role which worsens with the severity of preeclampsia in patients. Maternal serum CA-125 level can be high during early pregnancy and the postpartum period. The potential source for this elevation is the fetal chorion, amniotic fluid and maternal decidua, these increased serum levels of CA-125 during early pregnancy and immediately afterbirth indicate disintegration of maternal decidua as a potential source, that is, extension of decidual destruction and separation of trophoblasts from the decidua are proposed as the mechanism underlying the increased CA-125 levels[10].

It is assumed that preeclampsia is related to reduce trophoblastic migration into the maternal decidua, which leads to chronic inflammation within the placenta. This process may lead to increased expression of CA-125. Thus, it can be hypothesized that maternal serum CA-125 levels will be higher in females with severe preeclampsia than in other patients due to the increase in inflammatory process. 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 [11].

In the current study maternal serum concentration ofCA125 were positively correlated with proteinuria (r =0.936 p <0.001), this finding was in agreement with **Han and Karaman (2013)** who found the same correlation (r =0.789 p<0.001).Elevation of the maternal serum concentration of CA-125 level in severe preeclampsia more than mild preeclampsia and control group[12], also, it was in accordance with the findingofCebesoy and **Dikensoy (2009)**[6] who reported that the serum concentration of CA-125 was significantly higher in women with preeclampsia in comparison to healthy pregnant women and added that serum CA-125 in severe preeclampsia was significantly higher than mild preeclampsia. There was a positive correlation between CA-125, albumin level and mean arterial pressure (MAP).Gungor andYenicesu (2011) [13] compared CA-125 values of healthy and preeclampticwomen throughout a given time interval (from the middle of the second trimester to term) and documented that serum concentration of CA-125 did not differ with respect to either pregnancy outcome or gestational age. However, there was a trend toward an elevation in CA-125 concentration for pregnancies that are destined to develop preeclampsia.

The present study disagreed withSchrocksnadel et al (2000)who was the first to compare 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, they reported that there were no statistically significant differences or an increasing trend could be noted for CA-125[5].Previous study compared serum CA-125 concentration of 120 women with pathological outcome of pregnancy (spontaneous abortion, fetal death, intrauterine growth retardation, chromosomal and structural abnormalities, and preeclampsia/eclampsia) to those of 350 women with normal outcome of pregnancy. They confirmed that maternal CA-125 serum concentrations were significantly higher in the first and the third trimesters of pregnancy when compared to those in the second trimester, but not significantly different from those obtained in pathological pregnancies [14].

Danismanet al (2011) reported in their study that CA-125 is a biochemical marker which reflects the severity of the underlying inflammatory process in preeclampsia; it may be assumed that the extension of decidual destruction and failure of trophoblastic invasionin preeclampsia may induce the secretion of CA125 within placenta(9).Another explanation for elevation of maternal serum CA125 in females with severe preeclampsia may be due to the formation of ascites resulting from the decreased albumin level. The albumin level in females with severe preeclampsia was significantly lower than that in females with mild preeclampsia and normal pregnancies. The presence of ascites may lead to peritoneal irritation and increased CA-125 levels [10].

The current study revealed the blood pressure and all laboratory results were statistically significantbetween the control and studied groups, meanwhile, the difference between control and mild preeclampsia groups was significant only for systolic and diastolic blood pressure, serum uric acid,

creatinine and CA125, this finding agreed with that of (Danisman et al. 2011)[9].

Serum uric acid levels showed statistically significant differences between control, mild preeclampsia and severe preeclampsia groups in the present study. Karumanchi and Naljayan (2013) documented a correlation betweenhyperuricemia and the severity of the disease[15]. Many et al (1996)stated that decreased renal tubular excretion may be responsible for the rise in serum uric acid levels in preeclampsia[16], More recently, increased oxidative stress and formation of reactive oxygen species have been proposed as another contributing source of the hyperuricemia noted in preeclampsia.

In current study there was a strong correlation between CA125 with systolic blood pressure, diastolic blood pressure, proteinuria and serum uric acid, and it was moderately correlated with AST and serum creatinine and also shows a weak correlation with hemoglobin level, platelet count, ALT and urea. Ozat et al (2011) [17]found that serum CA-125 concentrations were correlated positively with systolic blood pressure, diastolic blood pressure, serum uric acid level and proteinuria. Moreover, they concluded that CA-125 is a biochemical marker of the severity of the underlying inflammatory process during preeclampsia. Thus, CA-125 seems to be a promising marker of preeclampsia.In the current study, the best cutoff value of CA-125 in severe preeclampsia was > 49.5, with a sensitivity of 82.5%, a specificity of 99%, a positive predictive value of 99%, a negative predictive value of 87.2% and area under the curve of 0.965% (0.94 – 0.989) as a marker of severe preeclampsia, this agreed with Ozat et al (2011)who found that the CA125 cutoff value of>50, serum CA-125 had a sensitivity of 97.2%, a specificity of 96% [17].

Conclusion:

SerumCA-125leveliselevatedsignificantly inmild and severepreeclampsia,itcorrelated with the severity of preeclampsia,soserum concentration ofCA125 maybeusedas a marker ofseverityof preeclampsia.

Conflict of interest

The authors declare that they have no conflict of interest.

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