

CA125 serum levels in Correlation with Preeclampsia severity

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Abstract:

Background

PET a disease of theories of unknown particular cause characterized by hypertensive disorder, protein excretion in urine that additionally could be accompanied or not by organ dysfunction. CA125 is an antigen measured by radioimmunoassay. Its physiological and molecular significance in obstetric diseases is not fully clarified most research trials are made on this antigen in obstetric research field to explore and investigate its role as a marker in various diseases.

Aim

The current research was performed to evaluate and correlate the correlation between CA125 serum level in normal gestations and gestations affected by PET.

Methodology

The current research study is composed of 300 singleton gestations. The study subjects were divided into 3 research groups: control research group (n = 100), mild PET research group (n = 100) and severe PET research group (n = 100). The three research groups were statistically alike as regards variables such as maternal age, gestational age and BMI. The research study was conducted at a private hospital in Jeddah, KSA, United Doctors Hospital. over 3 years from April 2014 to April 2017.

Results

The current research study results displayed that no statistical significant difference existed between the research study groups concerning age, BMI, parity, smoking, GA and serum creatinine. On the other hand SBP, DBP, serum urea, serum CA125, urine protein, and NICU admission were statistically significantly lowest in control research group followed by mild PET research group and statistically significantly highest in severe PET research group. Interestingly it has been revealed in the current research findings that platelets count was statistically significantly lowest in severe PET research group with no statistically significant difference between control and mild groups. The current research study have evaluated in addition diagnostic performance of laboratory investigations performed between research study groups displayed the following Serum BUN, serum CA125 and proteinuria had statistically significant high diagnostic performance and features in discriminating between PET from normal (highest in urine protein). On the other hand Serum BUN had statistically significant moderate diagnostic performance and features, whereas serum CA125 and urine protein had statistically significant high diagnostic performance and features in discriminating severe from mild PET (highest in urine protein).

Conclusions

Our research group came to the conclusion that serum CA125 level in maternal serum is directly correlated to PET presence and its degree of severity i.e CA-125 is a Biological marker mirroring the disease severity. Additionally it has the privilege of being. More readily available and considered less costly in comparison to other biological markers, It could be used as a screening tool for PET. However larger sample size should be considered in future research studies and consideration should be made for ethnic and racial difference that could aid in future met analysis performance.

Introduction

Hypertensive disorders of gestation is one of the common issues leading to maternal mortality globally. It is responsible for around 12% of maternal mortalities worldwide. Roughly 5% of gestations develop PET, which makes it one of the chief gestational medical disorders. The WHO statistically guessed that above 100,000 females pass away from PET every year all over the world, the issue is more prominent in developing countries in comparison to developed countries. 1-5 Maternal and fetal morbidity is great, particularly in developing nations having a prevalence range around 2% to 17%. As preeclampsia is a disease of theories having no well demarcated etiology featured clinically by hypertensive disorder, protein excretion in urine, +/- Organ function affection. In vast majority of case scenarios, pathological examination reveals microscopic evidence of placental vascular insufficiency correlated with other pathological developments such as placental inflammatory decidual vasculopathy, placental diffuse thrombosis, and/or abnormal invasive trophoblastic activity to the endometrial lining [6-10].

The pathophysiological pathways of PET are not well settled, although the chiefly accepted theoretical pathway is that of deficient trophoblastic invasive action of the placenta to deciduas causing endothelial cell insult, reduced intravascular volume, chronic inflammatory process, and affected vascular responsiveness [11-15].

The consecutive maternal adaptive pathway to gestational abnormal immunologic response to pregnancy is an immunological response against placental tissue and paternal derived antigens causing fetal hypoxia and inflammatory mediators secretion that have a negative impact on endothelium. A prominent inflammatory mediator secreted is the CA125 antigen. Clinically used in practice as a sensitive but nonspecific tumor marker in management protocols of ovarian malignancies. The value of CA125 in obstetric related diseases is not fully clarified as most research trials performed investigating its applicability are experimental in fashion [16-20]. In gestation, the fetal chorionic villi, amniotic fluid and decidua are possible biological sources and origin of CA125 antigen during the first trimester of gestation and during the period of puerperium with serum concentrations of CA125 elevating during the first gestational trimester and falling back to normal non-gestational range of values during the 2nd and 3rd gestational trimesters. Damage in decidual lining of cells due to chorionic villi invasive action during early gestation causes the CA125 originated from the decidual lining additionally that occurs during placental separation at delivery. Consequently, considering decidual destruction and trophoblastic separation from the decidual lining are cellular mechanisms for rise of CA125 in PET gestations [21-23].

Previous performed research came to a conclusion that the hypoalbuminemia occurring in PET gestations is considered contributing factor in rising serum CA125 concentration levels since reduced levels of albumin is correlated to clinical and subclinical edema and ascites in PET gestations. Another research group additionally displayed a rise in binding activity of CA125 antigen on immune cells of pregnant females and gestations with PET. The current research study aimed to assess and investigate the serum levels of CA125 in patients with and without PET and values its clinical applicability in the diagnosis pathway and prognostic power in PET [24,25].

Methodology

The current research study is a prospective research study conducted at private hospital in Jeddah, KSA, United Doctors Hospital after ethical approval from hospital ethical committee, over 3 years from April 2014 to April 2017. The research study was conducted on 200 singleton gestations having PET (Research study groups involving mild PET, severe PET).

Cases clinically diagnosed with PET after 32 gestational weeks have been enrolled for the research study group. While for the research control group (n=100), the gestations visiting the outpatient clinic the hospital for routine.

antenatal care visit after 32 gestational weeks were recruited. The 32nd gestational week was randomly used by the research group as an inclusive criterion. PET clinical diagnosis and classification as the bulletin of the ACOG. Hypertension was featured as an absolute blood pressure measurement [140/90 mmHg after 20 gestational weeks].

by at least two blood pressure 4 hours apart measurements. Protein in urine have been featured as 0.3 g protein excretion in urine. Exclusive research criteria have been presence of DM, chronic hypertensive disease, clear history of peripheral vascular disorder and/or antihypertensive medication and a BMI <19 or > 30 kg/m². Study Subjects were Divided into 3 research groups: control research group (n = 100), mild PET research group (n = 100) and severe PET research group (n = 100). The 3 research study groups were displayed and revealed as statistically Alike as regards maternal age, gestational age and BMI. Maternal blood samples for CBC, serum creatinine, Serum uric acid and serum CA-125 levels have been obtained by consistent phlebotomy withdrawal procedure from all study subjects after being recruited to the research study and control categorical groups. Obtained blood samples for CA-125 have been collected into anticoagulant-free glass test tubes, centrifuged instantaneously at 6,420 g (4 degree celcius) and stored without delay at -70 degree Celcius. Additionally, 24-hours urine have been gathered from each study subject to investigate the quantity of protein excreted in urine. Levels of CA 125 in serum have been measured by electrochemoluminescence immunoassay, however CBC indices have been obtained by an automated blood counter machine. Serum creat. and uric acid levels were assayed by an automatic chemical analyzer machine, TBA 40FR. The intra- and inter-assay statistical coefficients of variation (CVs) were reported to be 4 and 2%, consecutively for serum CA-125 assays obtained. The normal range was rated as 0–35 IU/ml as regards CA-125 serum levels. Patient age, parity, BMI, gestational age, SBP, DBP, treatment protocols, CBC indices and serum concentrations of uric acid, creatinine and CA-125, the expected fetal weight, the occurrence of intrauterine growth restriction and intrauterine fetal death for all study subjects were recorded.

Statistical analysis

The obtained data have been coded, tabulated, and statistically analyzed by using IBM SPSS statistics (Statistical Package for Social Sciences) software version 18.0, IBM Corp., Chicago, USA, 2009. Descriptive statistics were done for quantitative data as minimum & maximum of range in addition to mean ± SD (standard deviation) for quantitative normally distributed data, whereas it was done for qualitative data as number and percentage.

Inferential analyses was performed for quantitative variables using independent t-test in cases of two independent groups ANOVA test with post hoc Tukey test for more than two independent groups. In qualitative data, inferential analyses for independent variables were done using Chi square test for differences between proportions with post hoc Bonferroni test. The level of significance was taken at P value < 0.050 is significant, otherwise is non-significant.



Results

	Normal (N=100)	Mild (N=100)	Severe (N=100)	P
Age (years)	25.9±3.8	25.6±2.4	25.5±1.5	^0.507
BMI (kg/m ²)	25.1±1.3	25.3±0.9	25.2±1.4	^0.389
Parity	0.9±0.9	1.0±1.0	0.8±0.8	^0.311
Nulliparous	45 (45.0%)	42 (42.0%)	46 (46.0%)	#0.839
Smoking	8 (8.0%)	11 (11.0%)	15 (15.0%)	#0.293
GA (weeks)	35.4±1.2	35.2±1.1	35.3±1.1	^0.445
SBP (mmHg)	117.3±6.8a	145.5±5.7b	159.4±6.4c	^<0.001*
DBP (mmHg)	76.8±5.6 a	101.4±6.2 b	110.3±5.6c	^<0.001*
Platelets (x10 ³ /mL)	250.4±29.8 a	257.9±30.3a	182.8±45.5b	^<0.001*
Serum creatinine (mmol/L)	64.0±3.4	64.6±2.7	64.4±3.0	^0.366
Serum urea (mmol/L)	0.20±0.07 a	0.34±0.07b	0.46±0.10c	^<0.001*
Serum CA125 (IU/mL)	44.9±2.0 a	53.1±5.4b	64.2±2.0c	^<0.001*
Urine protein (gm/mL)	0.21±0.13 a	1.48±0.50b	4.57±0.99c	^<0.001*
Expected fetal weight(kg)	3.0±0.4 a	2.5±0.4b	2.1±0.3c	^<0.001*
Fetal birth weight (kg)	3.2±0.4 a	2.5±0.5b	2.1±0.4c	^<0.001*
IUFD	3 (3.0%)	5 (5.0%)	9 (9.0%)	#0.174
NICU admission	1 (1.0%) a	9 (9.0%)b	12 (12.0%)b	#0.009*

Table 1: Comparison between the studied groups

^ANOVA test with post hoc Tukey test, #Chi square test with post hoc Tukey test, *Significant, HG: Homogenous groups by post hoc test have the same letter(a,b,c)

Table (1) and figures (1)

Reveal and display that: No statistical significant difference between the research study groups as regards age, BMI, parity, smoking, GA and serum creatinine. However SBP, DBP, serum urea, serum CA125, urine protein, and NICU admission were statistically significantly lowest in control group followed by mild PET research group and significantly highest in severe PET research group. Fetal birth weight was statistically significantly highest in control research group followed by mild PET research group and statistically significantly lowest in severe PET in comparison to control group. Platelets count was statistically significantly lowest in severe PET research group with no statistically significant difference between control and mild groups. Expected fetal weight was statistically significantly highest in control group with no statistically significant difference between mild and severe PET research groups.

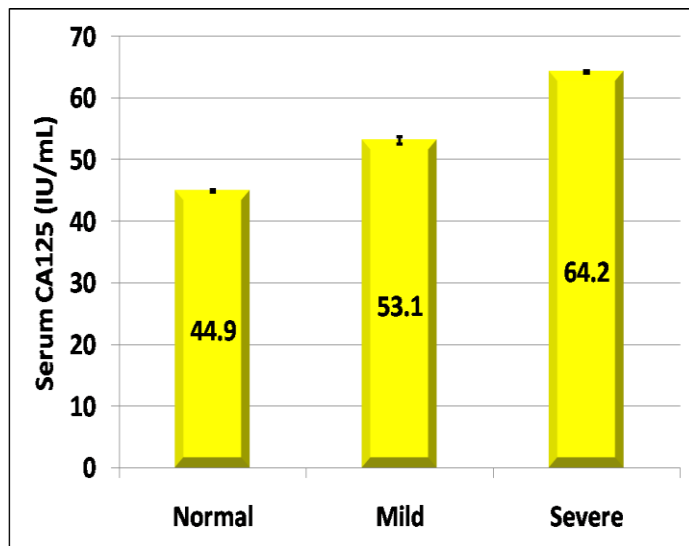


Figure 1: CA125 among the studied groups

Variables	Measure s	Normal (N=100)	Mild (N=100)	Severe (N=100)
Age	r	0.001	-0.035	-0.113
	p	0.989	0.732	0.263
BMI	r	-0.011	0.028	-0.029
	p	0.913	0.783	0.775
Parity	r	-0.102	0.424	0.049
	p	0.313	0.100	0.629
GA	r	0.102	0.022	-0.026
	p	0.312	0.828	0.796
SBP	r	0.144	0.116	0.037
	p	0.152	0.251	0.716
DBP	r	-0.059	0.124	0.004
	p	0.562	0.218	0.972
Platelets	r	0.008	0.096	-0.274
	p	0.941	0.343	0.006*
Serum creatinine	r	-0.042	-0.012	-0.174
	P	0.677	0.909	0.083
Serum urea	r	-0.147	-0.064	0.143
	p	0.145	0.529	0.156
Urine protein	r	0.096	-0.009	0.094
	p	0.340	0.928	0.355
Expected fetal weight	r	0.145	-0.134	-0.011
	p	0.149	0.184	0.913
Fetal birth weight	r	-0.061	-0.061	-0.105
	p	0.543	0.546	0.298

Table 2: Correlation between CA125 and other variables among study groups Pearson correlation, *Significant



Table (3) and figures (2) show that: Only CA125 had significant negative correlation with platelets in severe group.

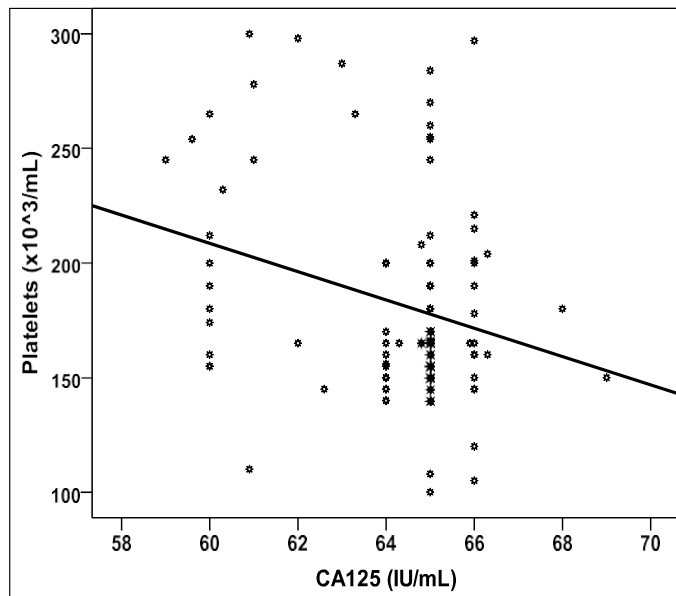


Figure 2: Correlation between CA125 and platelets among group.

Group	IUFD	Lived	P
Mild	58.8±1.6	52.8±5.4	^<0.001*
Severe	65.9±1.4	64.0±2.0	^0.006*

Table 3: Comparison between IUFD and lived fetuses regarding CA125 (IU/mL)

^Independent t-test

CA125 was significantly higher in cases with IUFD in mild and severe groups .

Lab	AUC	SE	P	95% CI	Cut off	Sensitivity	Specificity
PET from normal							
Serum creatinine	0.558	0.035	0.100	0.490–0.627	--		
Serum BUN	0.944	0.014	<0.001*	0.918–0.971	≥0.28	92.0%	89.0%
Serum CA125	0.931	0.016	<0.001*	0.901–0.962	≥48.8	88.5%	99.0%
Urine protein	1.000	0.000	<0.001*	0.000–1.000	≥0.8	99.5%	100.0%
Severe from mild							
Serum creatinine	0.477	0.041	0.568	0.396–0.557	--		
Serum BUN	0.856	0.029	<0.001*	0.800–0.913	≥0.41	77.0%	90.0%
Serum CA125	0.996	0.002	<0.001*	0.992–1.000	≥59.3	99.0%	95.0%
Urine protein	0.989	0.006	<0.001*	0.978–1.000	≥2.5	95.0%	98.0%

Table 4: Diagnostic performance of lab investigations in differentiation between research study groups

AUC; Area under curve, SE: Standard error, CI: Confidence interval, *Significant

Table (4) and figures (3,4) display that: Serum BUN, serum CA125 and urine protein had statistically significant high diagnostic performance and characteristics in differentiating PET from normal (highest in urine protein). On the other hand Serum BUN had statistically significant moderate diagnostic performance and characteristics, whereas serum CA125 and urine protein had statistically significant high diagnostic performance and characteristics in differentiating severe from mild PET (highest in urine protein).

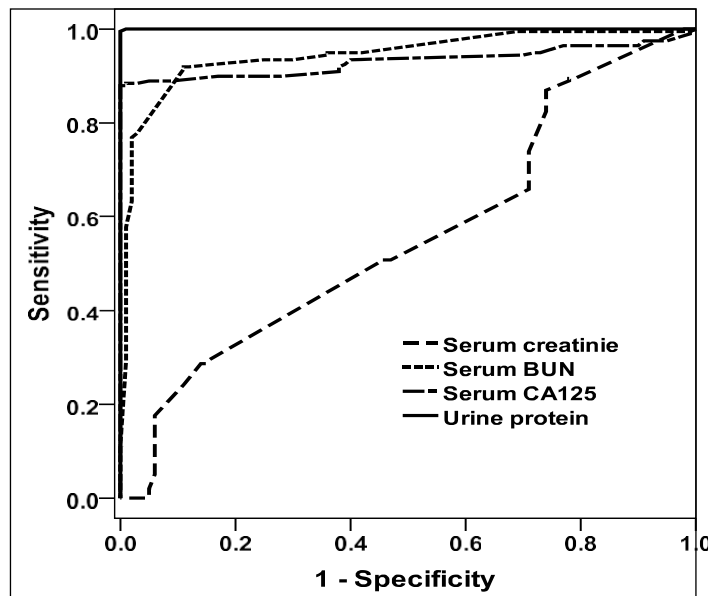


Figure 3: ROC curve for serum creatinine, serum BUN, serum CA125 and urine protein in differentiating PET from normal groups.

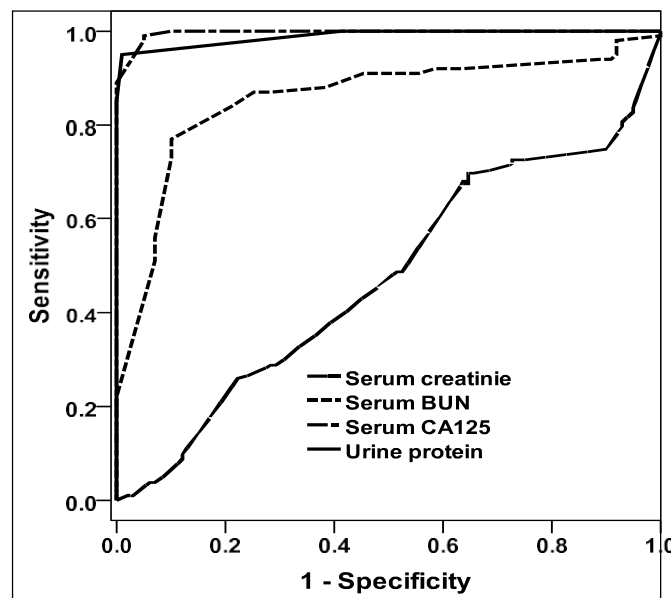


Figure 4: ROC curve for serum creatinine, serum BUN, serum CA125 and urine protein in differentiating severe from mild PET groups

Discussion

Various priorly conducted research studies have investigated the correlation between maternal CA 125 serum levels and PET, but these researches are mainly experimental, widely unapproved and the results are debatable showing great deal of conflict [1,3,5,7].



The current research study displayed that no statistical significant difference existed between the research study groups concerning age, BMI, parity, smoking, GA and serum creatinine. On the other hand SBP, DBP, serum urea, serum CA125, urine protein, and NICU admission were statistically significantly lowest in control research group followed by mild PET research group and statistically significantly highest in severe PET research group. Fetal birth weight was statistically significantly highest in control research group followed by mild PET research group and statistically significantly lowest in severe PET research group. Interestingly it has been revealed in the current research findings that platelets count was statistically significantly lowest in severe PET research group with no statistically significant difference between control and mild groups. Expected fetal weight was statistically significantly highest in control research group with no statistically significant difference between mild and severe PET research groups. Additionally when statistically comparing and contrasting between IUFD and live birth in correlation to serum CA 125 levels have shown that CA125 was significantly higher in cases with IUFD in mild and severe groups. The current research study have evaluated in addition diagnostic performance of laboratory investigations performed between research study groups displayed the following Serum BUN, serum CA125 and proteinuria had statistically significant high diagnostic performance and features in discriminating between PET from normal (highest in urine protein). On the other hand Serum BUN had statistically significant moderate diagnostic performance and features, whereas serum CA125 and urine protein had statistically significant high diagnostic performance and features in discriminating severe from mild PET (highest in urine protein). In a similar research approach fashion Schröcksnadel et al research group investigated the correlation between serum CA125 levels in cases with gestational hypertensive disorders, normally healthy gestations and normal non-gravid research control groups however did not find statistical significant difference between the three research categories [4-15]. Another research group additionally mentioned that although CA125 levels in maternal serum are revealed to be greater during the first and third gestational trimesters but did not show a correlation with PET but another research study, investigated serum CA125 levels in gestations with normal blood pressure and gestations that developed PET [17-24]. Revealing That serum CA125 levels did not vary as regards gestational outcome however they implied and observed a liability to elevation in serum CA125 levels for gestations that develop PET. Our current research, on the other hand, had findings in harmony with the Cebesoy et al. research group displaying a statistically significant greater levels of serum CA125 in gestations that developed PET. On the other hand it was suggested that the rise in CA125 levels in PET is due to ascites present in PET gestations due to hypoalbuminemia. The current research study displayed in a clear fashion that elevation of CA125 serum levels in PET gestations in comparison to gestations with normal blood pressure levels and in addition statistically significantly greater in cases suffering severe grade of PET, these observations are similar and inharmony with observations obtained by Karaman et al. research group [12-25]. A priorly performed research study studied 54 PET gestations/and 56 healthy gestations. The serum CRP and CA-125 serum levels.

were displayed to be statistically significantly greater in gestations with PET in comparison to healthy gestations. Additionally CRP and CA-125 serum levels in gestations with severe PET and eclampsia were statistically significantly greater than gestations with mild PET. Furthermore, statistical significant correlations have been revealed between CRP levels, serum albumin concentration, CA-125 serum levels and mean arterial blood pressure. The research group in that study concluded that CRP and CA-125 are potential biological markers in PET. This reveals the possible value of CA125 antigen as a biological marker or for uncovering of the prognosis of illness severity.

Various priorly performed research studies reveal that sFlt-1, PlGF, and sFlt-1/PlGF ratio as biological markers are not considered clinically simple, and are not of low-cost, due to financial and practical issues. While CA-125 is more readily available and considered less costly form of testing, therefore it is considered a promising biological marker for screening PET. The current research study has various limitations such as the sample size is small and the research should consider racial and ethnic differences that could have an influence on the disease severity [4,9,12].

Conclusion

Our research group concluded that raised levels of maternal serum CA 125 is correlated with the development of PET and that it have a role in reflecting disease severity. Therefore, our research group recommends future research to be performed on wider scale to confirm the findings of the current research study performed to reveal and uncover the clinical predictive value as a biological marker for PET in addition to determining a suitable cut-off level value particularly within cases having severe disease presentation. More prospective research is needed to reveal and clarify the precise pathological pathway of raised CA-125 serum levels in gestations with PET and to reveal the clinical value of CA-125 in PET.

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