EVALUATION OF SERUM CA-125 LEVEL IN NORMAL AND PRE-ECLAMPTIC PREGNANCIES IN SULAIMANI CITY

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ABSTRACT

Background

Pre-eclampsia 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 pre-eclampsia; however, the disease is multi-systemic affecting almost all systems of the body. CA125 has been found to be elevated in normal and pre-eclamptic pregnancies.

Objectives

To assess the level of CA-125 in normal and pre-eclamptic pregnancies to find out whether this marker is significantly elevated in women with pre-eclampsia, also to find out any correlation between the severity of pre-eclampsia and the serum concentration of CA 125.

Patients and Methods

This was a case control study, carried out in Sulaimani Maternity teaching hospital over a period of one year starting from the 1st of May 2015 to the 30th of April 2016. The study included 150 pregnant women, with singleton pregnancy in their 3rd trimester, these women were categorized into three group, fifty women with healthy pregnancy (the control group). Fifty women with mild pre-eclampsia and fifty women with severe pre-eclampsia (the study groups). The serum CA125 level was measured for the women in the three groups and comparison was made among them.

Results

Mean serum CA-125 and mean arterial pressure were significantly higher in the pre-eclamptic groups compared to the control group (P- value =0.0001). There was a direct correlation between CA-125 and mean arterial pressure in pregnant women with sever pre-eclampsia. The sensitivity and specificity of CA- 125 level were 94% for the detection of pre-eclamptic pregnancies.

Conclusion

Serum CA-125 was significantly higher in pre-eclampsia groups in comparison to the control group and the level was directly correlated with the severity of pre- eclampsia.

Keywords: *Pre-eclampsia; CA 125 level; Sever pre-eclampsia.*

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INTRODUCTION

Pre-eclampsia is a pregnancy-specific syndrome that affects virtually every organ system, characterized by the new onset of hypertension and proteinuria after 20th week of gestation in a woman whose blood pressure was previously normal [1, 2].

Pre-eclampsia may also occur up to six weeks' post-partum [3]. The disease can occur in the absence of fetal tissue (molar pregnancy), and in the absence of a uterus (abdominal pregnancy) [4], suggesting that it is the trophoblastic tissue that provide the stimulus for the disorder [5].

Hypertension in pregnancy defined as either, Diastolic blood pressure (DBP) > 110mmHg on any one occasion or DBP ≥ 90 mmHg on two or more consecutive occasions > 4 Hours apart. Proteinuria in pregnancy define as either one 24-hour collection with total protein excretion > 300 mg, or two, clean-catch-midstream, or catheter specimens of urine collected > 4 hours apart with ≥2+ on reagent strip [6]. Hypertensive disease complicates 6-12% of all pregnancies.

Pre-eclampsia occurs in approximately 3-5% of them [5]. Pre-eclampsia is the leading cause of maternal morbidity in developed countries and accounts for 15% of maternal death in Unites States [7]. In the UK, pre-eclampsia is the second largest cause of both direct maternal death and perinatal loss, responsible for the death of six to nine women annually [8]. More than10% of women will develop pre-eclampsia in their first pregnancy [9]. The recurrence risk in a subsequent pregnancy is 20 percent, but is much higher if severe pre-eclampsia developed at an extremely early gestation in the first pregnancy [10]. The exact nature of primary event causing pre-eclampsia is not known. Pre-eclampsia is disease of theories, because genetic, immunologic, vascular, hormonal, nutritional, and behavioral factors have all been proposed as causes [2]. No single definitive cause has been identified and the origin of the disease is considered to be multifactorial and both placental and fetal factors play a role. Those currently acceptable theories of the disease origin include: 1. Placental implantation with abnormal trophoblastic invasion of uterine vessels, 2. Immunological maladaptive tolerance between maternal, placental and fetal tissues, 3. maternal mal-adaptation to cardiovascular or inflammatory changes of normal pregnancy, 4. Genetic factors including inherited predisposing genes as well as epigenetic influences [11].

Regarding pathophysiology of pre-eclampsia, placental bed biopsies have demonstrated that trophoblastic invasion is patchy in these pregnancies and the spiral arteries retain their muscular walls. This is thought to prevent the development of a high flow, low impedance utero-placental circulation. The reason why trophoblastic invades less effectively in these pregnancies is not known but may reflect an abnormal adaptation of the maternal immune system. It is widely believed that defective trophoblastic invasion results in relative under-perfusion of the placenta and this releases factors into the maternal circulation that targets the vascular endothelium [2, 4]. The nature of this factor has not been identified, although numerous candidates have been proposed including a variety of growth factors, cytokines and products of oxidative stress caused by hypoxic-reperfusion injury in the placenta. As the target cell of the disease process, the vascular endothelial cell, is so ubiquitous, pre-eclampsia is a truly multisystem disease, affecting multiple organ systems concurrently [12,13].

CA-125 is a sensitive, but not specific, tumor marker used for the diagnosis and monitoring of patients with epithelial ovarian cancer. It has been found to be elevated in the serum of patients with various benign diseases like endometriosis [14]. It is a glycoprotein antigen which is located on cell surface. Fetal chorion, amniotic fluid and maternal decidua have been indicated as the potential sources of CA-125 in pregnancy. Serum concentrations of CA-125 are increased in early pregnancy and immediately after birth, implicating disintegration of the maternal deciduae as a possible source, that is, extension of decidual destruction and separation of trophoblasts from decidua are proposed as the underlying mechanism for the elevation in the serum of CA-125 during and immediately after pregnancy. The same mechanism can work out for the pregnancies which were complicated with pre-eclampsia. It has been assumed that the failure in trophoblastic invasion and the induction of an inflammatory process within placenta may trigger the expression and elevation of CA-125 level in pregnancies complicated by pre-eclampsia [15].

Aims of the study

1. To assess the level of CA-125 in normal and pre-eclamptic pregnancies to find out whether this marker is significantly elevated in women with pre-eclampsia.
2. To find out any correlation between the severity of pre-eclampsia and the serum concentration of CA 125.

PATIENTS AND METHODS

This is a case control study conducted in Sulaimani Maternity Teaching hospital over a period of one year starting from the 1st of May 2015 to the 30th of April 2016. The study included 150 pregnant women, with singleton pregnancy in their 3rd trimester (between 32-40weeks gestation), the participants were categorized into three group, fifty pregnant women with healthy pregnancy (the control group) who were attended the antenatal care unit. Fifty women with mild pre-eclampsia and fifty women with sever pre-eclampsia (the study groups), who were selected according to the clinical signs, symptoms& investigations and admitted to obstetric ward for evaluation. Pregnant women with BMI >30 $Kg/m^{2,}$ diabetes, chronic hypertension, renal disease cardiovascular disease and ovarian diseases were excluded from the study. The diagnosis of pre-eclampsia relied on blood pressure measurement of 140/ 90 mmHg on two consecutive readings 4 hours apart with patient kept at rest or one measurement of 160/110 mmHg or more and the presence of more than 1+ protein in urine by dipstick. All patient included in the study have a documented normal blood pressure level before 20 week of gestation. The diagnosis of severe pre-eclampsia was considered when the blood pressure was ≥160/110 with a proteinuria ≥ +2. Other concurrent parameters were: persistent headache, visual disturbances, Epigastric pain, impaired hepatic and renal function tests and thrombocytopenia.

A verbal consent was obtained from all women participated in the study. Complete examination (general and obstetric examination) was done for all patients and the following investigations were done for all women included in this study: general urine examination, complete blood count, liver function test, renal function test, serum CA-125 level, and an obstetrical ultrasound. For estimation of CA 125 level, 3ml of blood was taken from each patient. The samples were collected by venipuncture and serum was separated. Serum samples were stored at 2-8°C for 24 hrs, for longer periods the sample stored at -70 °C (this has been done in a special refrigerator in the laboratory, the analysis was performed within one month of collection. CA-125 was measured by enzyme-linked immunosorbent assay (ELISA), the level of CA 125 was then compared between the three groups.

RESULTS

The study included 150 pregnant women in their 3rd trimester of pregnancy, 50 women with healthy pregnancy, 50 women with mild pre-eclampsia and 50 women with severe pre-eclampsia. The three groups were comparable in their demographic characteristics as no statistically significant difference was found between the three groups with regard to their mean age, BMI and gestational age (P value >0.5) , Table 1

Table (2) shows the clinical &laboratory data which include the mean arterial blood pressure (MAP), Platelet count, Blood urea (mg/dl), Serum creatinine (mg/dl) and CA-125(IU/ml) in the control and study groups as following:

The mean of MAP in mild and severe pre-eclampsia was 112.6±3.6; 130.7±4.6 respectively which was significantly higher in comparison to the control group (86.1±6.8) as the P value was (0.0001). The mean platelet count in mild and severe pre-eclampsia groups was 196.0 ($1000/ml^3$) ±32.5, 172.1±30.1($1000/ml^3$) respectively, while in the control group was 219.7±35.9($1000/ml^3$). The difference was statistically significant (P value = 0.0001). The mean blood urea level in mild and severe pre-eclampsia was 26.2±7.7, 34.3±11.1 respectively which was significantly higher in comparison to the control group which was 14.5±5.1 (P value = 0.0001). The mean serum creatinine level in mild and severe pre-eclampsia was 0.8±0.1; 1.1±0.3 respectively which was significantly higher in comparison to the control group which was 0.7±0.1 (P value =0.0001). The mean level of CA-125 in mild and severe pre-eclampsia was 23.68±4.07; 34.57±7.06 respectively which was significantly higher in comparison to the control group (level =10.30±3.91), the P value was (0.0001).

Table (3) show coefficient correlation (r) of CA-125 with clinical &laboratory data in comparison between pre-eclampsia & control groups. There was significant and direct correlation between CA-125 level with MAP in severe pre-eclampsia as the (r) value was (0.427), while for the mild pre-eclampsia and control groups the coefficient correlation was not significant and inversely correlated as the (r) value was (-0.093, -0.172) respectively. There was a significant and inverse correlation between CA-125 level with the platelet count in severe pre-eclampsia as the (r) value was (-0.399), while in mild pre-eclampsia and control group the coefficient correlation was not significant and directly correlated as the (r) value was (0.015, 0.178) respectively.

Regarding the blood urea, there was significant and direct correlation with CA-125 in mild and severe pre-eclampsia as the (r) value was (0.474, 0.610) respectively while in the control group the coefficient correlation was not significant and directly correlated as the (r) value was (0.299). There was no significant and direct correlation between serum creatinine and CA-125 in mild, severe pre-eclampsia and control group as the (r) value was (0.106, 0.179, 0.075) respectively.

Figures 1 and 2 shows the Receiver operator characteristic curve. Depending on previous data, analysis was done to find the sensitivity and specificity of CA-125 test which was assessed by Receiver operator characteristic (ROC) curve to detect the significant level of CA-125 for prediction of pre-eclampsia. The ROC curve plots the sensitivity (true positive rate) against - specifity (true negative rate).

The ROC curve identified cut-off point of 17.165 IU/ml as a diagnostic test in pre-eclampsia with sensitivity and specificity of 94%, 94% respectively and the sensitivity and specificity of CA-125 for differentiation between mild and severe pre-eclampsia was86%, 86% respectively with cut-off point of 27.270IU/ml.

The Pearson correlation coefficient (r), * Correlation is significant at the 0.05 level. **correlation is significant at the 0.01 level, the r + is direct correlation r - is inverse correlation. The r value < 0.3 represent no correlation, The r < 0.5 mild correlation, r > 0.5 moderate strength, r > 0.7 strong correlation.

Table 1. Demographic characteristics of women in the study and control groups.

Character	Severe preeclampsia No. (50) Mean±SD	Mild preeclampsia No. (50) Mean±SD	Control No.(50) Mean±SD	P value
Age(years)	30.4±5.2	31.3±4.4	29.5±4.5	0.314
BMI(Kg/m^2)	24.3±3.4	23.8±1.8	23.6±2.9	0.670
Gestational age(weeks)	35.4±3.4	35.2±1.6	36.3±2.3	0.361

Table 2. The clinical & laboratory findings in the control and study groups.

Clinical and laboratory data (Mean±SD)	Severe preeclampsia No. (50)	Mild preeclampsia No. (50)	Control No. (50)	P value
MAP	130.7±4.6	112.6±3.6	86.1±6.8	0.0001*
Platelet count (1000/ml^3)	172.1±30.1	196.0±32.5	219.7±35.9	0.0001*
Blood urea (mg/dl)	34.3±11.1	26.2±7.7	14.5±5.1	0.0001*
Serum creatinine (mg/dl)	1.1±0.3	0.8±0.1	0.7±0.1	0.0001*
CA125 (IU/dl)	34.57±7.06	23.68±4.07	10.30±3.91	0.0001*

Table 3. Coefficient correlation (r) of CA-125 with clinical &laboratory data in comparison between pre-eclampsia & control groups.

		CA-125		
		Severe Preeclampsia	Mild Preeclampsia	Control
MAP	r	0.427**	-0.093	-0.172
	p	0.002	0.520	0.231
Platelets count	r	-0.399*	0.015	0.178
	p	0.043	0.920	0.217
Blood urea (mg/dl)	r	0.610**	0.447**	0.299
	p	0.0001	0.001	0.064
Serum creatinine (mg/dl)	r	0.179	0.106	0.075
	p	0.214	0.462	0.606

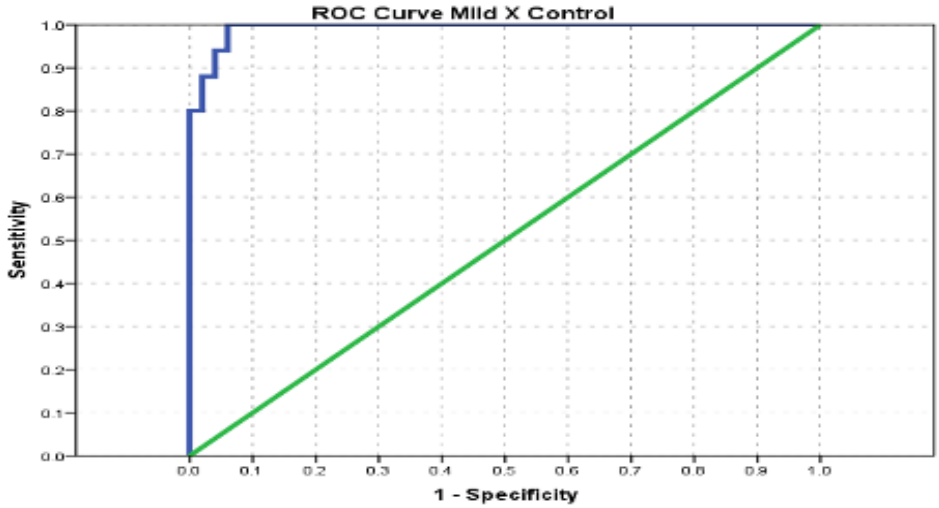

Figure 1. Receiver operating characteristics of CA-125 for mild pre-eclampsia and control group.

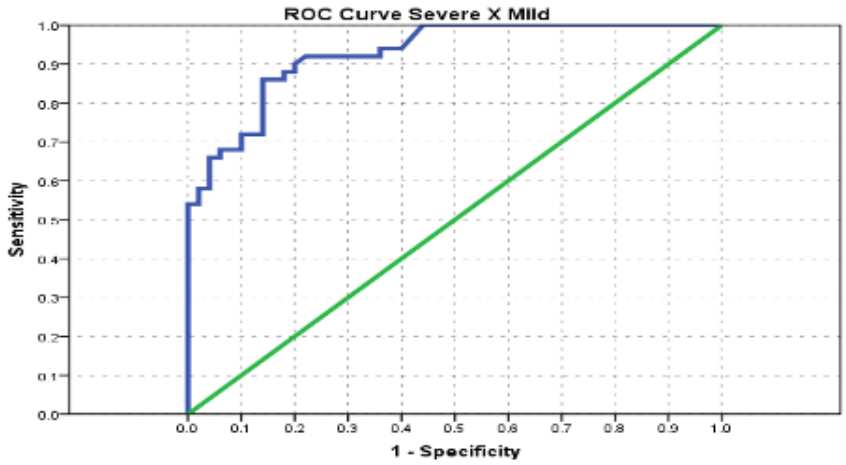

Figure 2. Receiver operating characteristics of CA-125 for severe & mild pre-eclampsia.

DISCUSSION

Pre-eclampsia 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 pre-eclampsia, but this disease may cause generalized damage to the maternal endothelium, kidneys and liver through the release of vasoconstrictive substances [16].

In the current study the MAP was significantly higher in the study group compared to the control group as the P value was (0.0001). This result agreed with Cebesoy et al (2009) [14] who showed high levels of MAP in pre-eclampsia groups compared to the control group. The current study showed that the platelet count was lower in the pre-eclampsia groups in comparison with the control group and the correlation was inverse and significant with severity of pre-eclampsia as the p-value was (0.0001). This finding is consistent with the following investigators: Cebesoy et al (2009) [14] who studied 54 women with Pre-eclampsia &eclampsia compared to 56 normotensive women taken as control; they found that mean platelet count was significantly lower in study group than control group. Also Ozat et al in (2010) [15] performed a study which included 242 women with mild & severe pre-eclampsia compared to 100 normotensive women taken as control, they found significant correlation between platelet count& the severity of pre-eclampsia.

The above finding is in contrast with finding of Seow et al (2005) [17] whose group found that the platelet count was not significantly different between the studied groups this is probably due to smaller sample size of their study.

Regarding the blood urea and serum creatinine we found that there was a significant increase in blood urea and serum creatinine in the pre-eclampsia groups in comparison with control group as the P-value was (0.0001) this increment was directly correlated with the severity of the disease.

The same results were observed by Pacarizi at el in (2012) [18], they studied the blood urea/ creatinine index as predictor of pre-renal damage in pre-eclampsia in 25 women with pre-eclampsia and 25 normotensive women; they found that there was significant increase in blood urea and serum creatinine levels in the study group in comparison with the control group. The same results were also observed by Manjareeka and Nanda in (2013). [19]

The current study showed that CA-125 level was significantly higher in mild and severe pre-eclampsia than control group as the P-value was (0.0001). Cebesoy et al (2009) [14] reported the same results, that the CA 125 increases with severity of pre-eclampsia. These results were also seen by Ozat et al. (2010) [15], they found that the CA-125 is a biochemical marker which reflects the severity of the underlying inflammatory process in pre-eclampsia.

While in Bon et al. (2001) [20] study, they assessed CA-125 and CA15-3 and compared their levels in 350 women with a normal pregnancy outcome and pathological pregnancies including pre-eclampsia, found that maternal serum levels of CA125 & CA15-3 were significantly higher in the first and the third trimester of pregnancy, but no significant difference was found between serum levels in normal pregnancy and those obtained in pathological one including pre-eclampsia patients. This finding probably due to different timing of measurement during pregnancy in their study (first & third trimesters) while the current study done on patients in third trimester.

Moreover, the current study showed that CA-125 level was found to be directly correlated with MAP and blood urea and inversely correlated with platelets count, which supports the relationship between severity of disease and CA-125 level.

In conclusion, the CA -125 was significantly higher in pre-eclampsia groups in comparison to the control group and this increment was directly correlated with the severity of pre-eclampsia. The results of this study support the use of serum CA-125 as useful predictive biomarker of pre-eclampsia. The use of serum CA- 125 level as screening test for pre-eclampsia with cut-off point of 17.165IU/ml and differentiation between mild and severe forms of pre-eclampsia with cut-off point of 27.270IU/ml.

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