Serum CA-125 in Ectopic Pregnancy

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ABSTRACT:

BACKGROUND:

CA-125 is a glycoprotein, its origin is uncertain during pregnancy. It rises during the first trimester and returns to a non-pregnancy range in late pregnancy.

OBJECTIVE:

To compare CA-125 levels between tubal ectopic and normal intrauterine pregnancy, and to find it's usefulness in differentiating intact from ruptured tubal ectopic pregnancy.

METHODS:

This prospective case-control study was carried out on sixty healthy women with single normal intrauterine pregnancy (NIUP) of 6-10 weeks gestation and sixty women with tubal ectopic pregnancy of same gestational age which were further subdivided into twenty-five women with ruptured tubal ectopic pregnancy (REP) and thirty-five women with unruptured tubal ectopic pregnancy (UREP). The levels of CA-125 were compared between these groups.

RESULTS:

The mean level of CA-125 in ruptured ectopic pregnancy group was 49.04±33.63 IU/ml and in unruptured ectopic pregnancy group was 24.3±16.89 IU/ml. The mean level of CA-125 in normal pregnant women (control group) was 53.95±31.2 IU/ml. There was a statistically significant difference between mean serum CA-125 levels of ruptured ectopic pregnancy and unruptured ectopic pregnancy group ($p< 0.05$), also there was a statistically significant difference between mean of CA-125 level of unruptured ectopic pregnancy group and control group ($p <0.05$), while there was no statistically significant difference between ruptured ectopic pregnancy group and control group ($p > 0.05$).

CONCLUSION:

CA-125 level is significantly elevated in ruptured tubal ectopic pregnancy than the intact tubal ectopic pregnancy, this increase in CA-125 levels can be used as additional test to identify tubal rupture.

KEY WORDS: CA-125 level, ectopic pregnancy.

INTRODUCTION:

Ectopic pregnancy remains a considerable cause of maternal morbidity and mortality worldwide [1,2,3]. Tubal ectopic pregnancies occur in 1-2% of pregnancies in the developed world and remain a leading cause of pregnancy-related first trimester deaths [2,4]. In the developing world, the incidence is much higher [5]. Currently it is diagnosed using a combination of transvaginal ultrasound and serial serum β-human chorionic gonadotrophin levels. Diagnosis is often delayed and these tests are time-consuming and costly, both psychologically to the patient and financially to health services. The development of a biomarker that can differentiate a tubal ectopic from an intrauterine implantation is therefore important [3]. Over 20 serum biomarkers have been identified to date in an attempt to permit earlier diagnosis of ectopic pregnancy, the instigation of earlier management and reduce healthcare costs [3,6]. The CA-125 tumour marker is a cell-surface antigen derived from the surface coelomic epithelium, including the mucosa of the entire female genital tract and maternal decidua. The fetal chorion, amniotic fluid and maternal deciduas contain significant amounts of CA-125 and represent practical sources of the elevated serum levels of the protein in pregnancy [7,8,9]. In normal intrauterine pregnancy, ruptured and unruptured tubal ectopic pregnancies, there are contradictory reports investigating the dynamics and comparison of maternal serum CA-125 levels [9,10,11.12].

The aim of the present study was to compare CA-125 levels between ectopic and normal intrauterine pregnancy and whether measuring CA-125 level can be used as an additional test in the differential diagnosis of intact and ruptured tubal ectopic pregnancy.

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MATERIALS AND METHODS:

This prospective case-control study was carried out in the Department of Obstetrics and Gynaecology, AL-Yarmouk Teaching Hospital, Baghdad, Iraq. The study was conducted over a period of twelve months starting from first of March 2011 to end of February 2012. A total of 120 pregnant women were enrolled in this study, 60 women with tubal ectopic pregnancy of gestational age 6-10 weeks, and further subdivided into two subgroups, ruptured and unruptured tubal ectopic pregnancy (patients group), and 60 healthy pregnant women with normal intrauterine pregnancy with a single viable pregnancy of the same gestational age (control group). The study was approved by the hospital's ethics committee, and all the women involved gave their informed consent to participate. All patients were collected from admitted cases to the Department of Obstetrics and Gynaecology and the out patients clinic of AL-Yarmouk Teaching Hospital. All intrauterine pregnancies were confirmed by transvaginal ultrasound. The diagnosis of ectopic pregnancy was suspected based on positive pregnancy test (serum β-hCG), urinary or β- hCG titre with a typical history and examination which included some or all of the following: abdominal pain, tenderness on pelvic examination, distended abdomen, adnexal mass and disproportionately small uterus. Furthermore, the diagnosis was based on positive visualization of an adnexal mass on TVS i.e. if one of the following three gray-scale findings were present, a heterogeneous mass or (blob sign) adjacent to and moving separately from the ovary, a mass with a hyperechoic ring around the gestational sac (bagel sign) and a gestational sac with a fetal pole with cardiac activity, i.e. a viable extrauterine pregnancy, combined with an abnormal serum β-hCG rise (<50% rise over 2 consecutive days), when the patient is vitally stable. In majority of cases, the final diagnosis of ectopic pregnancy was made by laparotomy, and in some cases by laparoscopy. Those patients who had a history of maternal conditions which would cause an increase in CA-125 level were excluded, including pelvic inflammatory diseases, endometriosis, uterine fibroids, endometrioma, lupus erythematosus, lung, liver, renal, pancreatic disease, and smoking. In addition, ectopic pregnancies with massive vaginal bleeding and intrauterine pregnancies with threatened abortion were excluded in the study. Eventually women in patients and control groups were subdivided into three groups:

1st group: 25 women diagnosed to have ruptured tubal ectopic pregnancy.

2nd group: 35 women diagnosed to have unruptured tubal ectopic pregnancy.

3rd group: 60 healthy pregnant women with single intrauterine pregnancy of the same gestational age to the previous two groups.

Serum samples from all 120 women were collected at the time of presentation. As soon as ectopic pregnancy was diagnosed, the CA-125 level was measured from the venous blood samples taken for the routine tests such as β-hCG, haemoglobin and hematocrit measurements. For the control group, blood samples were obtained from normal pregnancies with the same weeks of gestation to the ectopic pregnancies. Blood samples were centrifuged at 3,000rpm for 15 minutes and sera were stored at below -20°C until they were studied. Serum CA125 levels were measured by using a 2010 Elecsys kit (Roche Diagnostic GmbH, D-68298 Mannheim, USA) by the electrochemiluminescence immunoassay (ECLIA) method.

Statistical analysis:

Analysis of data was carried out using the available statistical package of SPSS-18 (Statistical Packages for Social Sciences- version 18). The significance of difference was tested using analysis of variance (ANOVA), independent student-t-test, Pearson Chi-square test (χ^2-test) and Pearson correlation. Statistical significance was considered whenever the P value was less than 0.05. In the differentiation of the groups, aiming to find the cut-off value of CA-125 levels, ROC analysis was performed. The levels in which the sensitivity and specificity is optimal have been determined as cut-off value.

RESULTS:

Table 1 shows the mean maternal age, parity, gestational age and body weight for the three studied groups. The mean maternal age for REP group was 29.00±5.21, while for UREP group was 28.57±6.19 and in NIUP group was 27.92±6.46). The mean parity for REP was 2.16±1.40, in UREP was 1.86±1.77 and in NIUP group was 1.85±1.61. The mean gestational age for REP group was 6.92±1.41, while for UREP group was 6.77±1.21, and in NIUP group was 6.62±1.57. The mean body weight for REP group was 64.7±1.22, while for UREP group was 66.6±3.66 and in NIUP group was 65±1.84. There was no statistically significant

difference among the three studied groups in maternal age, parity, gestational age and body weight (p>0.05). Table 2 shows the distribution of CA-125 levels for the REP group, UREP group compared to NIUP group. Regarding the CA-125 level, there was a statistically significant difference among the three studied groups (p=0.022). CA-125 levels in the unruptured tubal ectopic pregnancy group were mainly in the low side while higher values were obtained with ruptured tubal ectopic pregnancy and normal intrauterine pregnancy groups. The mean CA-125 level in REP group was 49.04±33.63 (with a range of 3-110), while for control NIUP group it was 53.95±31.2 (with a range of 3-122), both were higher than the mean of UREP group which was 24.3±16.89 (range 7-73). The mean CA-125 level in total tubal ectopic pregnancy was 34.58±27.86 (with a range of 3-110), this mean was lower than that of NIUP group (table 2). There was a significant difference in the mean of CA-125 between REP and UREP (P=0.0001), and also a significant difference between UREP and control group (P=0.0001), but there was no statistically significant difference in the mean of CA-125 level between REP group and control group (P=0.520). When the mean level of CA-125 was compared between total ectopic pregnancy (both ruptured and unruptured) and NIUP, there was a statistically significant difference between the two groups (P=0.0001) as shown in table 3. Table 4 shows the correlation of CA-125 level (IU/ml) with maternal age, Parity and gestational age for the three studied groups**.** There wasn't any statistically significant correlation between CA-125 levels and maternal age in the REP and UREP groups, but there was a positive weak correlation with the control group.

Regarding parity and body weight there wasn't any statistically significant correlation between CA-125 levels, parity and body weight for the three studied groups. There wasn't any statistically significant correlation between CA-125 levels and gestational weeks in the REP and UREP groups. Nevertheless, there was a significant negative correlation between CA-125 levels and gestational age (weeks) in the control group.

For further analysis of data the ROC curve was used in order to determine a cut-off value of CA-125 that can differentiate NIUP from ectopic pregnancy and from its both subgroups (ruptured and unruptured). Figure 1 shows the ROC curve of CA-125 as a diagnostic test for ectopic pregnancy (both ruptured and unruptured). According to the curve, for any given cut-off value there is low sensitivity and negligible specificity, this means that there is no cut-off value that can differentiate ectopic pregnancy from normal intrauterine pregnancy although there was a significant difference between the two groups (p=0.0001). From the ROC curve we found that it is helpful in the diagnosis (area 0.699) but there is no useful cut-off value of CA-125 as it is 98.3% sensitive at level 6.00 but with only 3.3% specificity and it is 50% sensitive at level 22.50 with also low specificity (15%). Figure 2 shows the ROC curve of CA-125 as a diagnostic test for ruptured ectopic pregnancy, also the curve can not determine a cut-off value that can differentiate REP group from normal intrauterine pregnancy because for any given cut-off value there is low sensitivity and low specificity, also no significant difference was found between the two groups (P=0.458). Figure 3 shows the ROC curve of CA-125 as a diagnostic test for unruptured ectopic pregnancy. According to the curve, for any cut-off value there is low sensitivity and negligible specificity, this mean that there is no cut-off value that can differentiate UREP group from NIUP group, although there was a significant difference between the two groups (P=0.0001). From the ROC curve we found that it is helpful in the diagnosis (area 0.804) but there is no useful cut-off value of CA-125 as it is 94.3% sensitive at level 7.50 but with only 3.3% specificity and it is 57.1% sensitive at level 17.50 with also low specificity (8.3%).

Table 1: The mean of maternal age (years), gestational age (weeks), parity and body weight (Kg) for the three studied groups.

	Ruptured tubal ectopic pregnancy	Unruptured tubal ectopic pregnancy	Normal intrauterine pregnancy	P-value
Age (years)	29.00±5.21 (20-37)	28.57±6.19 (17-42)	27,92±6.46 (19-44)	> 0.05
Parity	2.16±1.40 (0-5)	1.86±1.77 (0-6)	1.85±1.61 (0-6)	> 0.05
Gestational age (weeks)	6.92±1.41 (5-10)	6.77±1.21 (5-10)	6.62±1.57 (5-10)	> 0.05
Body weight	64.7±1.22(50-74)	66.6±3.66(52-90)	65±1.84(54-88)	> 0.05

-Data were presented as Mean ± SD (Range)

Table 2: The CA-125 level (IU/mL) distribution for the three studied groups.

CA-125 level (IU/mL)	Ruptured Ectopic (n=25)		Unruptured Ectopic (n=35)		Control (n=60)	
	No.	%	No.	%	No.	%
<10	2	8.0	6	17.1	2	3.3
10--	6	24.0	14	40.0	5	8.3
20--	1	4.0	3	8.6	7	11.7
30--	2	8.0	5	14.3	13	21.7
40--	1	4.0	4	11.4	4	6.7
50--	3	12.0	-	-	4	6.7
60--	3	12.0	2	5.7	5	8.3
70--	2	8.0	1	2.9	6	10.0
80--	1	4.0	-	-	4	6.7
90--	2	8.0	-	-	4	6.7
=>100 (IU/L)	2	8.0	-	-	6	10.0
MeanCA125(IU/mL) (Range)	49.04±33.63(3-110)		24.3±16.89 (7-73)		53.95±31.2(3-122)	
For the total ectopic pregnancy patients the mean CA-125 was 34.58±27.86 (3-110)						
X^2=37.58; P=0.022*						

Table 3: The P value between two variables and three variables using t-test and ANOVA test.

P value	Using ANOVA test	Using t-test for two independent means		
	All groups	Ruptured ectopic pregnancy X unruptured ectopic pregnancy	Ruptured ectopic pregnancy X Normal pregnancy	Unruptured ectopic pregnancy X Normal pregnancy
Age (years)	o.733	o.779	o.460	0.630
Parity	o.701	o.480	o.405	o.984
Gestational age (WK)	0.131	o.664	0.059	0.170
Body weight	0.641	0.230	0.752	0.230
CA-125 (IU/ml)	0.0001*	0.0001*	0.520	0.0001*

* Significant using ANOVA test for more than two independent means at 0.05 level of significance* Significant using Students-t-test for two independent means at 0.05 level of significance.

Table 4: The correlation of CA-125 level with maternal age, Parity, body weight and gestational age.

		CA-125 level		
		Ruptured Ectopic (n=25)	UnrupturedEctopic (n=35)	Control (n=60)
Age (years)	r	0.182	0.026	0.352*
	P	0.383	0.884	0.006
Parity	r	0.279	0.077	0.095
	P	0.178	0.660	0.472
Gestational age (weeks)	r	0.045	0.113	-0.619**
	P	0.832	0.517	0.001
Body weight (kg)	r	0.065	0.040	0.088
	p	0.870	0.212	0.544

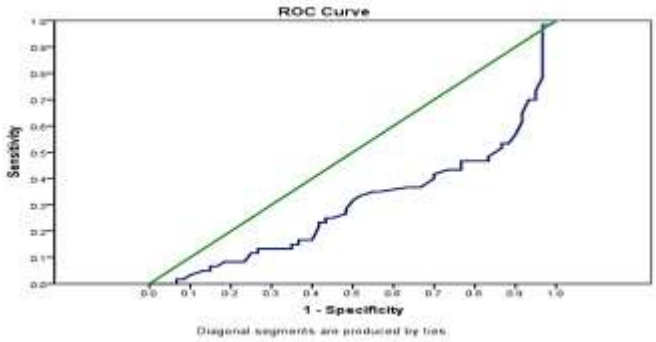

Figure 1: The ROC curve of CA-125 as a diagnostic test for ectopic pregnancy (both ruptured and unruptured).

Area under the Curve	Std. Error	P value	95% Confidence Interval	
			Lower Bound	Upper Bound
0.699	0.048	0.0001*	0.207	0.395

*Significant area

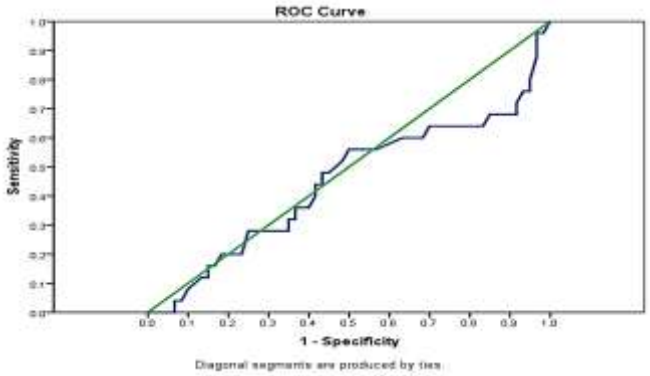

Figure 2: The ROC curve of CA-125 as a diagnostic test for ruptured ectopic pregnancy.

Area under the Curve	Std. Error	P value	95% Confidence Interval	
			Lower Bound	Upper Bound
0.551	0.073	0.458	0.305	0.592

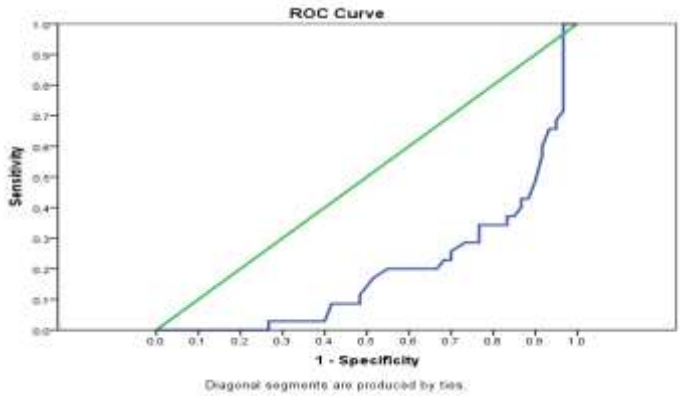

Figure 3: The ROC curve of CA -125 as a diagnostic test for unruptured ectopic pregnancy.

Area under the curve	Std. Error	P value	95% Confidence Interval	
			Lower Bound	Upper Bound
0.804	0.046	0.0001*	0.107	0.286

*Significant area

DISCUSSION:

Ectopic pregnancy is a relatively common complication, which can be fatal, if it is not promptly diagnosed. Early diagnosis presents an important challenge [13]. The prognostic predictive value of maternal serum CA-125 measurement was investigated in different studies with conflicting results. Although some studies indicate that serum CA-125 levels do not predict spontaneous miscarriage in the first trimester of pregnancy, there is inconsistent evidence regarding the use of CA-125 to distinguish between intrauterine and ectopic pregnancies [14-16]. In the present study the mean CA-125 level was high in NIUP group (53.95±31.2). This finding agree with Jacobs *et al.* [17] and Brumsted *et al.* [9], they found a high level of CA-125 in early pregnancy. This increase can be explained by the disintegration of maternal deciduas due to blastocyst implantation. In our study we found that mean CA-125 level of ectopic pregnancy group (both ruptured and unruptured) was significantly lower than that of NIUP group, this agree with findings reported by Kobayashi *et al.* [18] and Katsikis *et al.* [19] but disagree with Sadovsky *et al.* [8] who reported that women with EP (ruptured or unruptured) were more likely to have elevated levels of CA-125 than women with intrauterine pregnancies, this may be explained by small sample size in their study. The mean CA-125 level in both NIUP group and REP group were higher than that of UREP group, this low level of CA-125 in UREP group in our study may be explained by impaired interaction between fetal trophoblast and tubal mucosa, this finding agree with results reported by Predanic *et al.* [11]. Our findings partially agree with those reported by Sekhavat *et al.* [20] who studied CA-125 level in REP and UREP and compared them with NIUP group, CA-125 level was significantly higher in REP group than that in the NIUP group which disagree with our results, while both these two groups show higher levels of CA-125 when compared with CA-125 value in intact tubal pregnancy group which agree with our results. In early intrauterine pregnancy and unruptured ectopic gestations, Sauer *et al.* [21] were unable to demonstrate any significant elevation in CA-125 levels over the values of-non-pregnant controls which disagree with our study in terms of normal CA-125 level in early intrauterine pregnancy, moreover, they reported that there was a significant elevation in CA-125 levels in patients with ruptured tubal gestations which agree with our study. Other authors include Kuscu *et al.* 1993[22] and Schmidt *et al.* 2001[23], compared in their studies tubal ectopic pregnancy, spontaneous abortion, and normal intrauterine pregnancy, no significant difference were found in the CA-125 level between normal intrauterine pregnancy and ectopic pregnancy which disagree with our results. Our study also show that there was no significant correlation of CA-125 levels with gestational age in the REP and UREP groups, while it correlate negatively with gestational age in the control group. Possible explanation may be that the decreasing CA-125 levels are related to the progressive decrease in the trophoblastic invasion speed as the pregnancy progresses, this finding agree with those reported by Malatyalioglu *et al.* [24]

CONCLUSION:

CA-125 level is significantly elevated in ruptured tubal ectopic pregnancy when compared to intact tubal ectopic pregnancy, this increase can be used as indicator of early rupture.

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