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## Original Research Article

# Maternal serum CA-125 repeated measurement during pregnancy and how to use as a prognostic factor of first trimester pregnancy outcome

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### ABSTRACT

**Background:** The aim of this study was to estimate the prognostic efficacy of repeated measurement of maternal serum CA125 in first trimester threatened miscarriage.

**Methods:** Prospective case control study was conducted in the outpatient clinic. 100 pregnant women were divided into 50 women with normal course of pregnancy, and the other 50 were subdivided into 25 pregnant women with lower abdominal pain without vaginal bleeding and 25 presented with minimal vaginal bleeding. Repeated measuring of serum CA125 was done for each case on the 5<sup>th</sup>, 10<sup>th</sup> weeks of gestation.

**Results:** Findings of this study suggested the possibility of using serum CA-125 for determining the prognosis of first trimester threatened miscarriage with cut-off value of CA125 38.25 U/ml on the 5<sup>th</sup> week of gestation and 53 U/ml on the 10<sup>th</sup> week of gestation in patients presented with pain only but in patients presented with minimal vaginal bleeding the cut-off value of CA125 on the 5<sup>th</sup> week of gestation become 45.6 U/ml and 68 U/ml on the 10<sup>th</sup> week of gestation.

**Conclusions:** CA125, on its own, can discriminate between continued and non-continued pregnancy.

**Keywords:** CA125, Pregnancy, Threatened miscarriage

### INTRODUCTION

The CA-125 tumor marker is a cell-surface antigen derived from the surface coelomic epithelium, including the mucosa of the entire female genital tract and the germinal epithelium of the ovaries. The fetal chorion, amniotic fluid, and maternal decidua also have been shown to contain significant amounts of CA-125 protein, and represent potential sources of the elevated serum levels of the protein in pregnancy.<sup>1</sup>

High levels of serum CA-125 was noticed in patients with normal early pregnancy, spontaneous abortion, and hydatiform mole; but the levels were low in patients with tubal pregnancy, especially if there had been no uterine bleeding.<sup>2</sup>

Schmidt et al concluded that single serum measurements of CA-125 in symptomatic first trimester pregnancies failed to discriminate between spontaneous abortion, ectopic, and normal pregnancies; however recent study done by Yadav et al concluded that single raised maternal serum CA-125 value has best predictive value.<sup>3,4</sup>

Nevertheless, some studies have shown that serum CA-125 measurements failed to discriminate between EP, and normal pregnancy.

Therefore, we assessed the possibility of using maternal CA125 alone in one measurement and also in repeated measurements as a prognostic factor of early pregnancy miscarriage.

## METHODS

This prospective case control study was conducted in outpatient clinic at Al Zahraa University Hospital and was done in the period between October 2018 and December 2019.

Firstly, the study was conducted on 115 pregnant women in the outpatient clinic but 15 of them didn't attend at the 10<sup>th</sup> week of gestation so the end results were 100 pregnant women divided into: group I (control group): 50 pregnant women with normal course of pregnancy. Group II (cases group): 50 pregnant women subdivided into: group IIa: 25 pregnant women with lower abdominal pain without vaginal bleeding group IIb: and 25 presented with minimal vaginal bleeding. The groups were examined at 5<sup>th</sup> and 10<sup>th</sup> week of gestation and followed up till 12<sup>th</sup> week of gestation.

### *Inclusion criteria*

Intact single intrauterine gestational sacs were included in this study. Pregnant woman presented with threatened miscarriage in the form of recurrent attacks of minimal vaginal bleeding or lower abdominal pain.

### *Exclusion criteria*

Any uterine vaginal or cervical lesion that could explain the vaginal bleeding; multiple pregnancy; general causes of bleeding; any cause could affect CA-152 level in blood such as: endometriosis, uterine fibroids (benign tumors), pancreatitis, pelvic inflammatory disease, cirrhosis of the liver, benign and malignant ovarian cysts; additionally malignancies of the uterine tubes, endometrium, lung, breast, pancreas, gastrointestinal tract and lymphoma were also excluded.

Informed consent after explanation was obtained from every pregnant woman. Detailed history was taken then general, abdominal and vaginal examination were done. Blood sample was collected from every case for measuring the serum CA-125 level as follows: the patient needed not to be fasting and no special preparation was necessary. Five ml of blood were collected from a peripheral vein by venipuncture avoiding hemolysis into plain tubes (without anticoagulant). After clotting of the blood sample, the serum was separated from the cells by centrifugation within 2 hours from collection. The serum was separated and transferred to clean tubes by sterile pipette. A ticket with the patient name and number was placed on each tube. All samples were stored refrigerated at 2-8°C for 2 days or for 12 months at -20°C. Before assay, the sera were allowed to come to room temperature (15-28°C) and mixed by gentle swirling or inversion. Serum CA-125 concentrations were measured using the CanAg CA-125 ELISA assay (Fujirebio Diagnostics, Göteborg, Sweden). It is solid-phase, non-competitive immunoassay, based on the direct sandwich technique, and were run according to manufacturer's instructions. The appropriate controls were

within the ranges provided by the manufacturer for all runs. Each pregnant woman contact data including mobile number and address were documented and informed if any complication occurred, follow up was done in the outpatient's clinic to determine whether bleeding has stopped or continued. Specific date was scheduled to repeat TVUS examination for each case at 10<sup>th</sup> week of gestation. At 12<sup>th</sup> week of gestation each woman studied was seen to reevaluate and record if miscarriage happened or continued her pregnancy. The aborted cases below 10<sup>th</sup> week of gestation were not included in the study.

The data were collected in one hundred files. Each file contains pregnant woman history, report of first ultrasound scan at 5<sup>th</sup> week of gestation and 10<sup>th</sup> week then finally twelfth week scan in normal pregnancy or the exact gestational age at which abortion happened.

### *Statistical analysis*

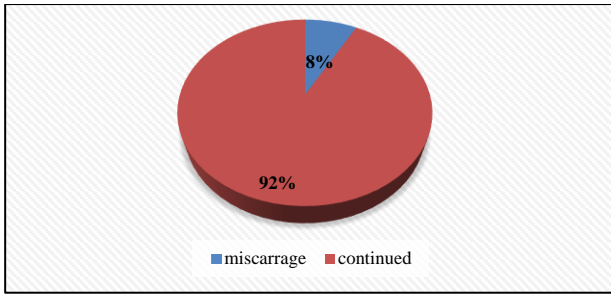
Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 20. Qualitative data were presented as number and percentages while quantitative data with parametric distribution were presented as mean, standard deviations and ranges. The comparison between two groups with qualitative data were done by using Chi-square test and/or Fisher exact test was used instead of Chi-square test when the expected count in any cell was found less than 5. The comparison between two independent groups regarding quantitative data with parametric distribution was done by using Independent t-test while comparison between two paired groups with parametric distribution was done by using paired t-test. The comparison between more than two independent groups regarding quantitative data with parametric distribution was done by using one way analysis of variance (ANOVA). Receiver operating characteristic curve (ROC) was used to assess the best cut off point with its area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p value was considered significant as the following: p>0.05: non-significant, p<0.05: significant and p<0.01: highly significant.

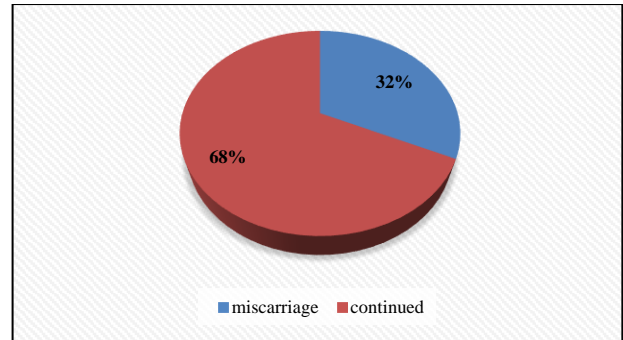
## RESULTS

Percentage of abortion in Group IIb was 32% which is the highest in comparison with group IIa 20% and in group I was only 8% (Figures 1, 2, 3).

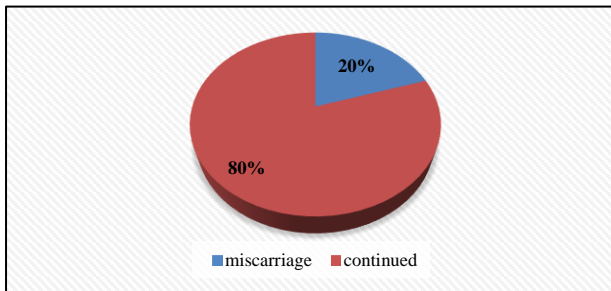
Highly statistically significant difference between CA-125 level in completed and aborted cases in group I at 5<sup>th</sup> and 10<sup>th</sup> week of gestation (Table 1). Also, there was highly statistically significant difference between CA-125 level in completed and aborted cases in group IIa at 5<sup>th</sup> and 10<sup>th</sup> week of gestation (Table 2).



**Figure 1: Percentage of miscarriage in group I (control group).**



**Figure 3: Percentage of miscarriage in group IIb.**



**Figure 2: Percentage of miscarriage in group IIa.**

The results of the ROC curve analysis demonstrate the high prognostic value of CA-125 at 5<sup>th</sup> week of gestation for pregnancy failure in group II a with a cut-off value of (38.25 U/ml) (Table 3) and at 10<sup>th</sup> week of gestation the highest sensitivity and specificity values of 100.00% were obtained with a cut-off value of 53 U/ml (Table 4).

There was highly statistically significant difference between CA125 level in completed and aborted cases in group IIb as well (Table 5).

**Table 1: Comparison of gestational sac, yolk sac diameter (mm), fetal heart rate (b/m), crown rump length (mm) and CA-125 (U/ml) in the women studied at 5<sup>th</sup> and 10<sup>th</sup> week of gestation.**

Total number (100)		Group I (n=50)	Group IIa (n=25)	Group IIb (n=25)	One way ANOVA	
		Mean±SD	Mean±SD	Mean±SD	F	P value
CA125 (U/ml)	At 5 <sup>th</sup> week	16.29±12.24	17.96±10.69	26.84±18.02	7.495	0.024
	At 10 <sup>th</sup> week	23.23±16.58	28.49±12.68	36.44±18.72	5.506	0.005

**Table 2: Comparison of CA-125 level in the completed and aborted cases in group I at 5<sup>th</sup> and 10<sup>th</sup> week of gestation.**

Total no.=50		Continued (n=46)	Abortion (n=4)	Independent t-test	
		Mean±SD	Mean±SD	t	P value
CA125 (U/ml)	At 5 <sup>th</sup> week	13.44±6.28	49.00±17.46	-9.113	0.000
	At 10 <sup>th</sup> week	20.29±9.62	68.37±35.53	-6.762	0.000

It shows highly statistically significant difference between completed and aborted cases in group I at 5<sup>th</sup> and 10<sup>th</sup> week of gestation.

**Table 3: Comparison of CA125 level in the completed and aborted cases in group IIa at 5<sup>th</sup> and 10<sup>th</sup> week of gestation.**

Total no.=25		Continued (n=20)	Abortion (n=5)	Independent t-test	
		Mean±SD	Mean±SD	t	P value
CA125 (U/ml)	At 5 <sup>th</sup> week	5.85±3.55	43.68±45.71	-3.475	0.002
	At 10 <sup>th</sup> week	11.69±6.86	69.29±64.16	-3.771	0.001

It shows highly statistically significant difference between completed and aborted cases in group IIa at 5<sup>th</sup> and 10<sup>th</sup> week of gestation.

**Table 4: Sensitivity, specificity, PPV, NPV of CA-125 in group IIa at 5<sup>th</sup> week of gestation.**

Parameters	Criterion	AUC	Sensitivity	Specificity	+PV	-PV
CA-125 at 5 <sup>th</sup> week (U/ml)	>38.25	1.000	100.00	100.00	100.0	100

At a cut-off value of CA125 (38.25 U/ml) the highest sensitivity and specificity values of 100.00% were obtained.

**Table 5: Sensitivity, specificity, PPV, NPV of CA125 in group IIa at 10<sup>th</sup> week of gestation.**

Parameters	Criterion	AUC	Sensitivity	Specificity	+PV	-PV
CA-125 at 10 <sup>th</sup> week (U/ml)	>53	1.000	100.00	100.00	100.0	100

A cut-off value of 53 U/ml CA125 gives sensitivity and specificity values of 100.00%

**Table 6: Comparison of CA-125 level in the completed and aborted cases in group IIb at 5<sup>th</sup> and 10<sup>th</sup> week of gestation.**

Total no.=25		Continued (n=20)	Abortion (n=5)	Independent t-test	
		Mean±SD	Mean±SD	t	P value
CA-125 (U/ml)	At 5 <sup>th</sup> week	14.07±10.24	77.94±11.51	-12.198	0.000
	At 10 <sup>th</sup> week	20.93±15.02	113.95±21.23	-10.607	0.000

It shows highly statistically significant difference between completed and aborted cases in group II b at 5<sup>th</sup> and 10<sup>th</sup> week of gestation.

**Table 7: Sensitivity, specificity, PPV, NPV of CA-125 in group IIb at 5<sup>th</sup> week of gestation.**

Parameters	Criterion	AUC	Sensitivity	Specificity	+PV	-PV
CA-125 at 5 <sup>th</sup> week (U/ml)	>48.6	0.923	75.00	100.00	100.0	89.5

At a cut of value of CA-125 (48.6 U/ml) the sensitivity and specificity were 75.00% and 100.00%.

**Table 8: Sensitivity, specificity, PPV, NPV of CA-125 in group IIb at 10<sup>th</sup> week of gestation.**

Parameters	Criterion	AUC	Sensitivity	Specificity	+PV	-PV
CA-125 at 10 <sup>th</sup> week (U/ml)	>68	0.958	85.71	94.12	85.7	94.1

CA-125, at a cut-off value (68 U/ml) the sensitivity and specificity were 85.71% and 94.12% respectively.

The results of the ROC curve analysis demonstrate the high prognostic value of CA-125 at 5<sup>th</sup> week of gestation for pregnancy failure in group IIb with a cut-off value (48.6 U/ml) the highest sensitivity and specificity values of 100.00% were obtained (Table 6) and at 10<sup>th</sup> week of gestation with a cut-off value of 68 U/ml the sensitivity and specificity were 85.71% and 94.12% respectively (Table 7).

## DISCUSSION

In 2017 a study was done by Eid et al concluded that CA-125 and progesterone are good predictors for the outcome me of 1<sup>st</sup> trimester of pregnancy in both normal women and those with threatened abortion. Both have excellent specificity and good sensitivity in prediction of the outcome.<sup>5</sup>

CA-125, β HCG and progesterone are good biochemical markers and FHR and CRL are good ultrasonographic markers for the prediction of outcome in women with threatened abortion. FHR at 110 bpm gives the best predictivity followed by serum P at 25 ng/ml, β HCG at 19887 mIU/ml, CA-125 at 80 IU/ml and CRL at 21 mm with the least predictive accuracy among studied markers. Adding serum progesterone to FHR gave a sensitivity and specificity of 100%.<sup>6</sup>

At 2001 it was proved that CA-125 maternal serum level increases during early first trimester of pregnancy than that

in nonpregnant women.<sup>7</sup> And that this elevation is exaggerated in cases with threatening symptom to the extent that the patient who presented the highest level of the antigen did abort later.<sup>8</sup>

This was explained by the fact that CA-125 molecules are found in abundant quantities in cytosolic fraction of decidual cells. During early gestation, chorionic villi invade the decidual cells, also in case of abortion the decidual cell destruction leads to release of CA-125 molecules into the maternal blood stream.<sup>9</sup>

Therefore, measurement of maternal serum CA-125 in cases of threatened abortion could be useful to determine the extent of decidual destruction which is directly related to the eventual outcome of pregnancy.

In the present study the mean serum level for CA-125 in all studied cases was (16.29±12.24) U/ml for group I at 5<sup>th</sup> week of gestation and was (23.23±16.58) U/ml at 10<sup>th</sup> week of gestation. In group IIa the mean serum level for CA-125 was (17.96±10.69) u/ml at 5<sup>th</sup> week of gestation and was (28.49±12.68) U /ml at the 10<sup>th</sup> while in group IIb the mean serum level for CA-125 was (26.84±18.02) U/ml at 5<sup>th</sup> week of gestation and was (36.44±18.72) U/ml at the 10<sup>th</sup> week of gestation. Additionally, our study demonstrated that serum CA-125 level in the study group IIa and IIb was significantly higher than that in the control group as shown in Table 1.

While, in group I the mean of CA-125 in the cases continued pregnancy was (13.44±6.28 IU/ml) and in cases ended by abortion was (49.00±17.46) at 5<sup>th</sup> week of gestation and at 10<sup>th</sup> week the mean was (20.29±9.62 IU/ml) and (68.37±35.53) respectively shown in Table 2. In group IIa the mean of CA-125 in the cases continued pregnancy was (5.85±3.55 IU/ml) and in cases ended by abortion was (43.68±45.71) at 5<sup>th</sup> week of gestation while at 10<sup>th</sup> week the mean was (11.69±6.86 IU/ml) and (69.29±64.16) respectively shown in Table 3.

In the present study as regard group IIa with a cut of value of CA125 (>38.25 U/ml) and (>53.00 U/ml) at 5<sup>th</sup> and 10<sup>th</sup> week of gestation respectively, sensitivity and specificity were 100.00% as shown in Tables 4 and 5.

As regards group IIb the mean of CA-125 in the cases continued pregnancy was (14.07±10.24 IU/ml) and in cases ended by abortion was (77.94±11.51) at 5<sup>th</sup> week of gestation while at 10<sup>th</sup> week the mean was (20.93±15.02 IU/ml) and (113.95±21.23) respectively shown in Table 6.

In group IIb, at a cut of value (>45.6 U/ml) at 5<sup>th</sup> week of gestation, sensitivity and specificity were 75.00% and 100.00% respectively. And at 10<sup>th</sup> week of gestation with a cut of value of CA-125 (>68 U/ml), sensitivity and specificity were 85.71% as shown in Tables 7 and 8.

This is in agreement with a study done by Mohamady et al 2016 as they reported that the use of certain maternal serum markers (CA-125 and progesterone) in the first trimester represent noninvasive, early and fast methods that can be considered as a good predictor for the outcome of pregnancy in cases with threatened abortion.<sup>10</sup>

They also reported that CA-125 level above 31.2 IU/ml predicted occurrence of miscarriage with an overall accuracy of 99.4%. Similar to these results, Fiegler et al, in a study on 200 consecutive women with spotting, viable ultrasound picture of the embryo in the uterus and gestational age ranging from 4-12 weeks, found that CA-125 levels were significantly higher in patient with threatened abortion 57.4±10.0 U/ml in comparison with control group 14.3±4.0 U/ml and also they were significantly elevated in pregnancies terminating eventually in spontaneous abortion 84.7±30.7 U/ml than those who continued 33.2±14.8 U/ml their pregnancies.<sup>11</sup> They also mentioned that women with symptoms of imminent abortion who have a CA-125 level of ≥43.1 U/ml should be considered as having a greater risk of miscarriage and patients with bleeding of ≥3 days should have a threshold value of 66.5 U/ml applied as a risk determinant. They concluded that a single serum CA-125 level determination is valuable in women with imminent abortion presenting with abdominal pain, vaginal bleeding or both.

Also in a similar study for Ghoneim et al in a study on 88 patients with threatened abortion in the first trimester classified into continued and non-continued group stated

that the mean serum levels of CA-125 were (76.59 and 137.45 U/ml) for both group respectively and were found to be significantly higher in non-continued group.<sup>12</sup>

The present study showed that a significantly higher CA-125 levels in intrauterine pregnancies complicated by abortions compared normal intrauterine pregnancies, reinforcing the majority of previous similar studies done by Katsikis et al and Schmidt et al.<sup>1,3</sup>

And lastly Salem et al on their study on 60 patients with threatened abortion divided into continued and non-continued groups reported that serum CA-125 were significantly higher in non-continued (79.1 IU/ml) than in continued group (36.2 IU/ml) and they concluded that a single serum measurement of CA-125 is an excellent positive test in cases of threatened first trimester miscarriage.<sup>13</sup> However, the cut-off reported in this study is lower than that reported by Scarpellini et al and Ghoneim et al who considered a cut-off level of 120U/ml.<sup>12,14</sup>

Azogui et al considered 125 U/ml as a cut-off level and it is significantly lower than that mentioned by Jerome et al, who considered a serum level of 150 U/ml as a cut-off level.<sup>15,16</sup>

This discrepancy between our cut off value and their cut off value was due to, they did not exclude the patients conceived by IVF (in vitro fertilization) from their study and also by the presence of high percentage of chromosomal abnormalities, confirmed by chromosomal studies of aborted fetuses.

There are many theories that explain the access of the decidual CA-125 to the maternal circulation, the most logic theory explaining the compartmental distribution of the CA-125 during pregnancy was presented by Ocer et al who stated that CA-125 molecules are found in abundant quantities in the cytosolic fraction of decidual cells. During early gestation, chorionic villi invade the decidual cells, while at term, mechanical disruption of decidual cells occurs at the time of placental separation. During these two events, decidual cells release the CA-125 molecules into maternal blood stream, explaining the two peaks of serum CA-125 in maternal circulation during the 1st trimester and immediately after labor and also with abortion. Otherwise, CA-125 molecules are preferentially secreted into the amniotic fluid.<sup>17</sup>

Our study showed that a measurement of serum CA-125 in a period between (5-10) weeks of gestation in patients suffering from vaginal spotting or bleeding is a good predictor of pregnancy outcome.

This study has some limitations. Causes of high CA-125 was only ruled out by history and examination however no documented baseline CA-125 was done for the pregnant ladies before pregnancy. Therefore, another study should consider preconceptional measuring of CA-125 level.

## CONCLUSION

In conclusion, the findings of this study suggest the possibility of using serum CA-125 alone for the prognosis of first trimester threatened abortion with cut-off value of CA-125 38.25 U/ml at 5<sup>th</sup> week of gestation and 53 U/ml at 10<sup>th</sup> week of gestation in patients presented with pain only but in patients presented with minimal vaginal bleeding a cut-off value of CA-125 at 5<sup>th</sup> week of gestation become 45.6 U/ml and 68 U/ml at 10<sup>th</sup> week of gestation.

CA-125 alone can discriminate between continued and non continued pregnancy especially if repeated at 5<sup>th</sup> and 10<sup>th</sup> week of gestation.

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