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Role of serum CA125 levels in predicting the outcome of threatened abortion

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Abstract
The purpose of the present investigation was to evaluate the prognostic role of serum CA125 in patients of threatened abortion and to find the cut off levels of maternal serum CA-125 in foreseeing the pregnancy results in patients with threatened abortion. 60 patients complaining of vaginal bleeding or spotting in first trimester were recruited and their outcome was evaluated at 20 weeks. The study was done on the women aged 20-40 yrs with gestation age between 7 to 14 weeks. The study revealed that CA 125 levels estimation is an appropriate tool in predicting outcome of threatened abortions. The ROC graphs gives the cut off level of 60 IU/ml in predicting the risk of abortion, with the sensitivity of 72%, specificity of 88.8%, PPV of 72%, NPV of 88% and accuracy of 89.83%. Thus making CA 125 clinically important in predicting the outcome of patients with threatened abortion at an early stage of gestation.

Keywords: threatened abortion, CA 125, first trimester bleeding

Introduction
Threatened Abortion is a clinical terminology that applies to women who are under 20 weeks Gestation having vaginal spotting or bleeding, a closed Cervical os and potentially mild uterine contraction with ensuing ultrasound scan confirming fetal cardiovascular movement. It is accounted for to happen in around one-fifth of pregnancies [1]. However, an expected 3 – 16% of these pregnancies with or without treatment, result in incomplete, complete, missed or septic abortion. Threatened miscarriage is an extremely worrisome condition for female, both physically and mentally. Some of the time, episodes of bleeding may continue for a considerable length of time or weeks, making the expectation of the result of pregnancy vital to ease the stress from both the patient and the doctor.

CA-125 can be used as a predictive marker for subsequent outcome of pregnancy. CA-125 (cancer antigen 125, carcinoma antigen 125, or carbohydrate antigen 125) is cell surface high molecular weight glycoprotein present in tissue derived from embryonic coelomic [2]. It has been found in high concentration in human amniotic fluid with amnion being major source of it.

During pregnancy, disruption of the epithelial basement membrane of the fetal membrane or disruption of the decidua could theoretically lead to rise in maternal CA 125 level, thus can be used as a predictor of subsequent spontaneous abortion. Its levels are increased in early pregnancy and immediately after birth [3], thus implicating the disintegration of the maternal decidua (i.e., blastocyst implantation and placental separation) as a possible source of the tumor marker elevation [4]. Therefore the elevated serum CA 125 levels in women with threatened abortion implicate poor outcome in future. This test is rather sensitive in determining the progression to the pregnancy loss.

Material and Methods
This prospective hospital based observational study was conducted in department of Obstetrics & Gynaecology Sawai Man Singh Medical college Jaipur (Rajasthan) from April 2017 to 2018. It included 60 patients complaining of bleeding per vaginum as study population.

Inclusion criteria
Included the women of age group between 20-40 years with gestation age ranging from 7 to 14 weeks. The patients with singleton pregnancy and presenting with vaginal bleeding or spotting

with ultrasonography signs of viable pregnancy were selected.

Exclusion criteria

Pregnant women with past history of Medical disorders in pregnancy, Gynecological disease, Uterine malformations, History of recurrent miscarriages, Chronic pelvic infection and endometriosis Conception by assisted reproductive techniques.

Method

The cases were selected from the inpatient and outpatient department of obstetrics and gynaecology unit of SMS Medical College and attached hospitals, having complain of vaginal bleeding with gestation age between 7 to 14 weeks and satisfying the inclusion criteria. An informed written consent was obtained from the participants.

The characteristics of all the patients related to their age, gravidity, period of Gestation, Ultrasonographic results were determined and data were collected. They were subjected to detailed history taking, complete general physical examination, systemic examination and obstetric examination. Their blood samples were taken and sent for Complete blood count, liver function test, renal function test, ABO Rh, viral markers, serum CA 125 levels. All participants were subjected to sonographic examination to confirm gestational age, fetal viability, intrauterine single gestation. All women in the study group were followed prospectively from their first appointment upto 20 weeks of gestation and patients were subdivided into 2 groups Group (A): continued their pregnancy Group (B):those who aborted. Outcome data were obtained from the hospital notes and confirmed by telephonic follow up wherever necessary.

Sampling procedure

5 ml of venous blood was collected from each patient for measuring CA-125 serum level. After clotting of the blood sample the serum was separated from the cells by centrifugation within 1 hour of collection and removed using sterile pipette. All samples were stored refrigerated at 2-8 ºC. Serum levels of CA-125 were assayed by chemiluminescent immunometric method using ADVIA Centaur.

Statistical analysis

Continuous variable will be summarized as mean and standard deviation whereas nominal/categorical variables as proportion (%). Unpaired t test, one way ANOVA test and tukey HSD test will be used for comparison of continuous variables while chi square test/fissure exact test will be used for nominal/categorical values.

ROC curve analysis will be done to assess appropriate cut off of Serum CA 125 to differentiate between abortion cases versus non-abortus.

P value less than 0.05 will be taken as significant. MEDCALC 16.4 version software will be used.

Result

On evaluating, the population constituted 60 patients with complain of bleeding per vagina. On assessing the outcome at 20 weeks of pregnancy, 18 of 60 (30%) pregnancies ended up in abortion, whereas 42 (60%) participants continued their pregnancy. Mean age of the total study population was 25.62±3.65 years which is the peak reproductive age group.

There was not much significant difference between the patients who aborted and who continued the pregnancy on the basis of age and residence. Maximum number of patients in were primigravida (53.3%). Out of the 18 aborted patient, 8 (44.4%) were primigravida and 10 (55.56%) were multigravida. The patient who continued the pregnancy also had similar distribution, 57.14% were primigravida and rest 42.7% were multigravida. There was no statistical difference in distribution of patients based on parity and gestational weeks. (Table 1)

Among patients of threatened abortion who aborted, mean maternal serum CA 125 level was 34.75 IU/ml and patients of threatened abortion who progressed normally to the period of viability had mean maternal serum CA 125 level of 148.01IU/ml. Statistically the difference was significant with the p value of <0.000. (Figure 1).

Table 1: Distribution of study population.

		Continued	Aborted	P value
Age (years)		24.23±3.53	24.33±3.06	0.621 NS
GA (weeks)		9.7±1.52	9.28±1.30	0.235 NS
Gravidity	1	24(57.14%)	8(44.44%)	0.664
	2	11(26.19%)	6(33.33%)	
	>=3	7(16.67%)	4(22.23%)	
Parity*	P0	27 (64.28%)	7 (38.88%)	0.163 NS
	P1	8 (19.04%)	7 (38.88%)	
	P2	7 (16.68%)	4 (28.24%)	
Hormonal levels	CA.125(IU/ml)	48.36±36.94	116.28±81.04	< 0.0001 S

Data are presented as mean ± S

NS - not significant.

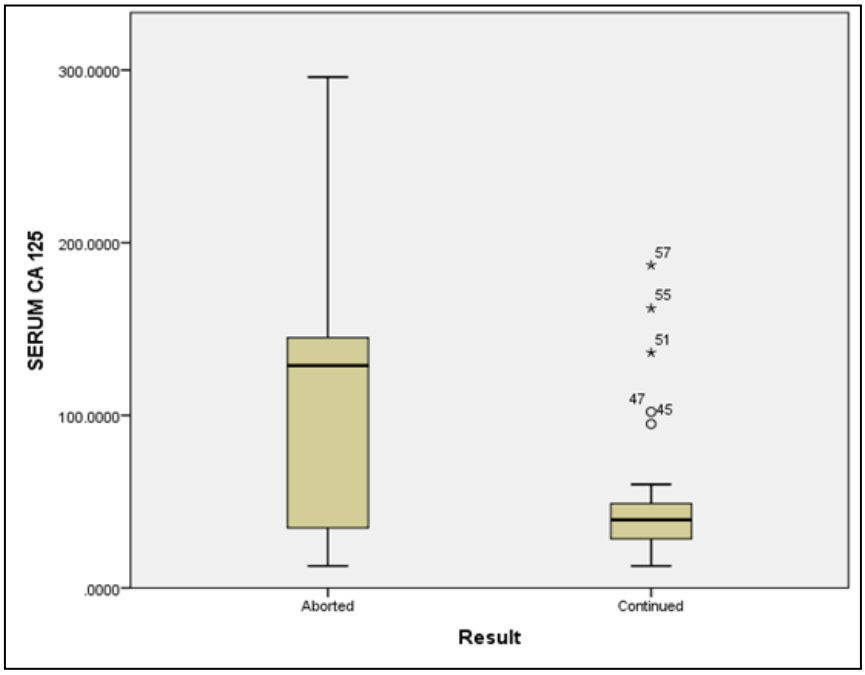

Fig 1: Maternal serum CA 125levels (IU/ml).

The ROC graphs gives us the cut off level of 60 IU/ ml in predicting the risk of abortion, with the sensitivity of 83.33%, specificity of 92.62%, PPV of 83.33%, NPV of 92.68 and accuracy of 89.93. Thus making CA 125 clinically important in predicting the outcome of patients with threatened abortion at an early stage of gestation. (Figure 2)

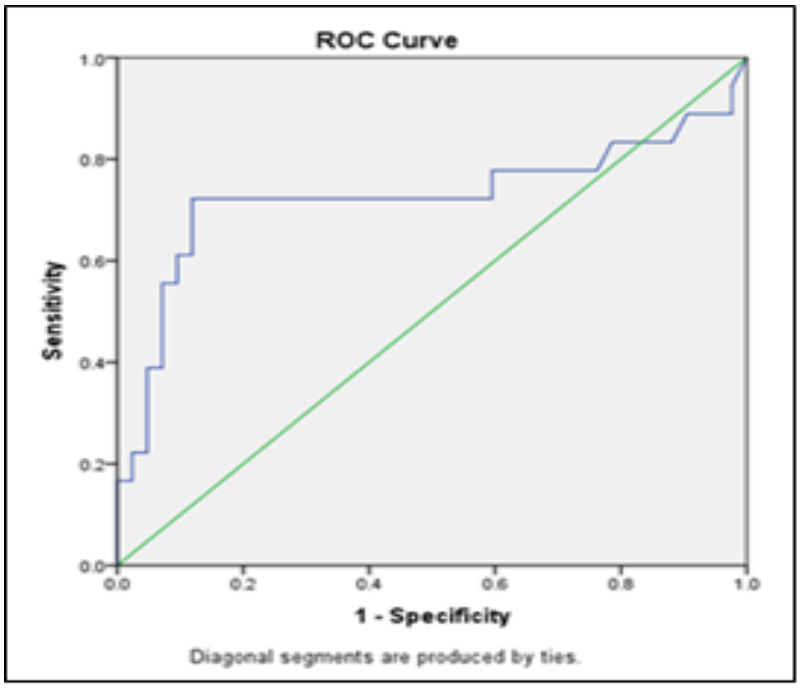

Fig 2: ROC Curve

Table 2: Distribution of study population according to maternal CA 125 levels

CA 125 (in IU / ml)	Result		Total
	Aborted	Continued	
> 60	13	5	18
	72.2%	27.8%	100.0%
<=60	5	37	42
	11.9%	88.1%	100.0%
Total	18	42	60
	30.0%	70.0%	100.0%
Chi-Square = 21.829, p = 0.000			

As shown in Figure 1 and Table 2, taking 60 IU/ml as cut off limit. 72.2% of patients of threatened abortion with maternal serum CA 125 level of more than 60 IU/ml aborted while 27.8% of patients of threatened abortion with maternal serum CA125 level of more than 60 IU/ml continued to the period of viability. Among patients of threatened abortion with serum CA 125 level lesser than or equal to 60 IU/ml, 11.9% of patients aborted while 88.1% of patients continued to the period of viability. Statistically the difference was significant with p value of <0.001.

Discussions

In this prospective study, we have focused on a very specific group of patients, those with complain of threatened abortion. Namely, those who had uterine bleeding in the presence of sonographically visible fetal heartbeat. In the present work, we found statistically significant increase of CA125 in aborted patients when compared to patients that continued their pregnancy after 20 weeks (48.36±36.94 and 116.28±81.04respectively). In addition, the sensitivity of CA125 in prediction of abortion in studied females was 83.33% and specificity was 92.62% at a cutoff value of > 60 IU/ml.

Our study can be compared with the work of Abd-Elrau of M Oun *et al* (2018) [5]. Their study included 110 women with manifestations of first trimester threatened miscarriage. CA 125 levels ranged from 8 to 77 IU/ml, and there was statistically significant decrease of CA125 in group (A) (continued) when compared to group (B) (aborted) (19.45±5.57 vs 53.83±9.48 respectively). As regard to sensitivity of different studied variable in prediction of threatened abortion, the best was CA125, with a sensitivity of 100% and specificity of 98.8% at cutoff value > 35 IU/ml. Concluding CA125 as a good screening tool in patients with threatened miscarriage to predict pregnancies who developed to complete abortion. It had the advantage of being available and cheap test that can be used in screening and follow up of management in patients with threatened abortion. In agreement with the results of the present work, (Al Mohamady *et al*. (2016) [6] reported that, the level of serum CA-125 for the threatened miscarriage (miscarried) group was 54.28±11.4 IU/ml; while for the threatened miscarriage (continued) group it was 18.81 ± 8.02 IU/ml. The difference was statistically significant (P<0.001). They added, using a ROC curve for CA-125 in predicting the outcome of pregnancy in threatened miscarriage cases, the cut-off limit of 31.2 IU/ml of CA-125 level achieved sensitivity of 96.2% and specificity of 100%. CA-125 level above 31.2 IU/ml predicted occurrence of miscarriage with an overall accuracy of 99.4%

Furthermore, results of the present work are comparable to those reported by Mohamed S. Sweed (2016) [7] who assessed the predictive value of single measurement of maternal serum CA-125 for pregnancy outcome in threatened miscarriage. Using Receiver-operating characteristic (ROC) curve analysis, optimal cut- off criteria of CA-125 > 58 IU/ml for prediction of occurrence of miscarriage in patients with threatened miscarriage was established with sensitivity of 78% and specificity 97%.

Results of Marwa Eid *et al* (2017) [8] also showed that women who continued their first trimester of pregnancy showed a significantly lower level of CA 125 when compared with those who aborted. (34.9±11.053 vs. 61.9±19.21, P = 0.022). The sensitivity, specificity, PPV and NPV of CA 125 predicting occurrence of abortion were 80.66, 100, 100, 95. 4% respectively. Concluding CA125 is a good predictor for the outcome of first trimester of pregnancy in both normal women and those with threatened abortion.

Several cut-off values were suggested in other studies in order to predict pregnancy outcome in early viable pregnancies complicated by vaginal bleeding. In this study, a cut-off limit of 60 IU/ml of CA-125 level was suggested, with a sensitivity of 83.33% and specificity of 92.62%. Fiegler *et al*. (2003) [9] used a cut-off value of 66.5 IU/ml with a sensitivity of 55%. Schmidt *et al*. (2001) used 65 IU/ml as a cut-off value and reported a sensitivity of 50% for this level. Azougi *et al*. (1996) used a 125 IU/ml as a cut-off value and reported a 100% sensitivity and specificity.

We have examined the potential value of serum CA 125 in predicting the future of a pregnancy in question. A proper prediction of how the pregnancy ends in a patient with symptoms of an abortive miscarriage allows shortening the time of hospitalisation, reducing the symptomatic and emotional problems resulting from waiting for the result of treatment.

Conclusion

Bleeding in early pregnancy can be a bewildering experience for any pregnant women, up to 50% of such pregnancies are usually lost. The evaluation of maternal serum CA-125 levels allowed us to discriminate better between the pregnancies with a poor outcome and those with a favourable outcome.

Reliable prediction of abortion in the first trimester could potentially improve pregnancy outcomes because it would allow closer prenatal monitoring, earlier diagnosis, and expeditious interventions. The next challenge for clinician researchers is to determine probably different cut off levels of serum CA 125 to validate the findings and widen the scope of CA-125 prognostic tool in threatened pregnancies.

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