Role of Serum CA125 Levels in Predicting the Outcome of Threatened Abortion

Hanan Samir Mahmoud [1*], Magdy Abdel-Mohsen Olama[2], Mona Amin Elhawary[3]

1 M.B.B.C.H Faculty of Medicine,Mansoura University, Egypt.

2 Professor of obstetrics and gynecology, faculty of medicine for Girls, Al-Azhar University, Egypt.

3 Lecturer of Obstetrics and Gynecology, Faculty of Medicine for Girls, Al-Azhar University, Egypt.

*** Corresponding author:** Hanan Samir Mahmoud ElSayed[1], Mona Amin Elhawary[2]

E-mail: hanansamir5050@yahoo.com, mona21up@hotmail.com

Abstract

Background: Vaginal bleeding prior to the 20th week of pregnancy is considered a threatened abortion. During the first two trimesters, around 25% of pregnant women have some vaginal bleeding, and 50% of these cases end in the pregnancy being lost. A spike in the mother's CA 125 level during pregnancy may result from disruption of the decidua or the fetal membrane's epithelial basement membrane, and this might be utilized as a predictor of a future spontaneous abortion.

Objective: To assess serum CA125's predictive value in patients who are facing an abortion threat.

Patients and methods: This was prospective case control study conducted on 80 ladies complaining of threatened abortion at Al-Zahaa University hospitals and Dikirnis General Hospital. Patients were split into two groups. Group A normal pregnancy, group B threatened abortion.

Results: There were statistically substantial variation between control group and threatened abortion group as regards CA-125 p<0.001, as most cases (87.5%) in threatened abortion group had higher CA-125 >35.12 compared to control group. Serum CA-125 level can significantly determine patients with threatened abortion with sensitivity and specificity was 77.5% and 79.5% when the cutoff point was >35.12 IU/ml

Conclusion: Serum CA125 is a valid and reliable predictor of pregnancy outcome in patient with threatened abortion, the levels are correlated to US finding, it has a sensitivity 77.5 & specificity 79.5 when cutoff point was >35.12 IU/ml.

Key words: Serum CA125, threatened abortion, pregnant women.

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Introduction:

Vaginal hemorrhage before 20 weeks of pregnancy in the presence of a positive urine and/or blood pregnancy test, a closed cervical os, no passage of the products of conception, and no indication of fetal or embryonic death is considered a threatened abortion. The World Health Organization (WHO) defines a threatened abortion as any bleeding within the first half of pregnancy that is not associated with cervical dilatation or bloody vaginal discharge linked to pregnancy.(1).

Threatened, inevitable, incomplete, full, septic, and missed abortions are among the varieties of spontaneous abortion. (2).

The cell surface high molecular weight glycoprotein known as CA-125 (also known as carcinoma antigen 125, carbohydrate antigen 125, or coelomic antigen 125) is found in tissue derived from embryonic coelomic and decidua. Amnion is the main source of this high concentration substance seen in human amniotic fluid. (3).

Its rise during the early stages of pregnancy and just after delivery suggests that the breakdown of the mother decidua—that is, the implantation of the blastocyst and the separation of the placenta—may be the cause of the elevated tumor marker. (4).

A spike in the mother's CA 125 level during pregnancy may result from disruption of the decidua or the fetal membrane's epithelial basement membrane, and this might be utilized as a predictor of a future spontaneous abortion. (5).

Patients and Methods

Eighty women who reported being threatened with abortion at Dikirnis General Hospital and Al-Zahaa University hospitals participated in this prospective case control study.

Study approval: Prior to commencing the study, the protocol and all related paperwork were submitted for ethical and research approval by the OB/Gyn department's ethics committee at Al Azhar University for females, in compliance with the applicable local regulations.

Sample size

The G power program was used to determine the sample size, the statistical test was Student's t-test with power 80%, significant level 5%, effect size 64%, and allocation ratio control to case 1, to be 40 threatened abortion women (cases) and 40 healthy pregnant (controls). Participants were split into two groups: Group (A): 40 women with normal pregnancy and Group (B): 40 women with threaten abortion with vaginal bleeding.

Inclusin criteria: Pregnant women aged between 20-40 years, gestation age ranging from completed 6 to 10 weeks calculated from last menstrual period at first time evaluated, follow up to 14week, pregnant women presenting with vaginal bleeding or spotting with positive pregnancy test and single pregnancy for group B

Exclusion criteria: Age more than 40 years old, pregnant individuals with a medical background who are expecting, pregnant women with uterine malformations, Patient diagnosed with ectopic or molar pregnancy, history with endometriosis and Pregnant women with ovarian cyst or tumors.

Methods

Intervention:

Each and every sufferer endured the following:

History taking: Date of birth, medical history: diabetes, anemia, hypertension, preeclampsia, others, history of prior surgeries, symptoms indicating threatening abortion, parity, Gravida, mood of previous delivery, history of sibling death, history of previous abortion and frequency, time of gestation.

General examination

Trans vaginal U/S

When inserting the transvaginal transducer GE logic sonography, particular attention was paid to the image's orientation. The probe was positioned either against the external cervical OS or in the distal vagina. By moving the probe side to side, from one adnexa to the next, sagittal imaging was acquired. The probe displayed a transverse/semi-coronal orientation when it was turned 90°. Moving the probe from anterior to posterior allowed for further imaging to be carried out. As a preliminary assessment, a general survey was carried out by moving the probe from the midline to the lateral borders at the bilateral adnexa. After that, the probe was turned 90 degrees and moved anteriorly and posteriorly.

Lab investigation

Routine investigation of first trimester was done

CA-125 assessment: CA-125 was measured in first visit and repeated it in the threatened abortion women who continued pregnancy to 14w in group B. Follow up of the selected patient to 14 weeks of gestation age was done.

Test principle

Sandwich principle: Each patient had 5 milliliters of venous blood drawn in order to measure their serum level of CA-125. The test took eighteen minutes total.First incubation: A sandwich complex consisting of 20 μL of sample, a monoclonal CA 125-specific antibody that has been biotinylated, and a monoclonal CA 125-specific antibody that has been labeled with ruthenium complexa is formed. Second incubation: The complex binds to the solid phase by the interaction of biotin and streptavidin after the addition of streptavidin-coated microparticles. The microparticles are magnetically attracted to the electrode surface of the measurement cell upon aspiration of the reaction mixture into it. After that, unbound materials are eliminated using ProCell/ProCell M. A photomultiplier is used to measure the chemiluminescent emission that is induced when a voltage is applied to the electrode. A master curve supplied by the reagent barcode or e-barcode and an instrument-specific calibration curve produced via 2-point calibration were used to determine the results.

Statistical analysis of the data

SPSS version 23 was utilized for data processing; data were verified, input, and examined. For qualitative variables, the data were reported as a number and a percentage, and for quantitative variables, as mean + standard deviation (SD). The used tests were: The difference between the quantitative variables in the two groups' non-normally distributed data was calculated using the Mann Whitney test. To compare the proportion of result between the two groups, use the Z-test for percentages. Utilized to determine the correlation between row and column variables is the chi-square test (X2). The odds ratio, or OR, is a statistical measure that contrasts the likelihood of an occurrence of a disease in persons with a certain characteristic or who have been exposed to a risk factor with the likelihood of the illness occurring in those without that characteristic or without exposure to a risk factor.

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Results

Table (1): Comparison of personal traits and demography between the two groups

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Variable		Group (A) Control group (N=40) No.	Group (A) %	Group (B) Threatened abortion group (N=40) No.	Group (B) %	Test value	P-value	Sig.
Age (year)	Mean± SD	25.98±3.98		25.85± 4.83		ZMWU= 0.261	0.794	NS
	Median	26.0		25.5				
	Range	20.0- 35.0		2.0- 37.0				
BMI (Kg/m2)	Mean± SD	31.96± 3.42		31.69± 2.44		T= 0.345	0.731	NS
	Median	31.15		31.5				
	Range	27.34- 43.16		26.92- 35.20				
Gravidity	G1	13	32.5%	17	42.5%	X2= 1.20	0.549	NS
	G2	14	35.0%	10	25.0%			
	>G2	13	32.5%	13	32.5%			
	Mean± SD	2.13± 1.07		2.08± 1.19		ZMWU = 0.434	0.664	NS
	Median	2.0		2.0				
	Range	1.0 - 5.0		1.0 - 5.0				
History of previous abortion	No	38	95.0%	38	95.0%	X2= 0.0	1.00	NS
	Once	1	2.5%	1	2.5%			
	Twice	1	2.5%	1	2.5%			
	Mean± SD	0.08± 0.35		0.08± 0.35		ZMWU = 0.0	1.00	NS
	Median	0.0		0.0				
	Range	0.0 - 2.0		0.0 - 2.0				
Smoking	No	40	100.0%	40	100.0 %	-	-	-
	Yes	0	0.0%	0	0.0%			
Gestational age (weeks)	Mean± SD	8± 1.22		8± 1.52		ZMWU = 1.858	0.063	NS
	Median	8		7				
	Range	6.57- 10.0		6.57- 10.0				

P value< 0.05 is significant, p≤0.01 is highly statistically significant, ZMWU = Mann- Whitney U test, T = Student T test, X2= Chi- Square test

There were no statistical substantial variations between control group and threatened abortion group as regards age, BMI, gravidity, history of previous abortion and gestational age p>0.05. (Table 1)

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Table (2): Comparison between the two groups as regard laboratory results and imaging criteria.

		Group (A) Control group (N=40)	Group (B) Threatened abortion group (N=40)	Test value	P-value	Sig.
Full blood count						
Hemoglobin (g/dl)	Mean± SD	10.93± 0.74	10.89± 0.53	T= 0.244	0.808	NS
	Median	10.85	10.85			
	Range	9.21- 12.90	9.90- 12.10			
WBCs (g/dl)	Mean± SD	7.72± 1.68	8.02± 1.21	ZMWU= 4.745	0.081	NS
	Median	7.40	7.99			
	Range	4.88- 13.3	4.5- 10.80			
Platelets count (g/dl)	Mean± SD	228.78± 58.02	236.16± 31.68	ZMWU = 0.891	0.373	NS
	Median	231.0	237.5			
	Range	106.0- 408.0	178.0- 300.0			
Urine analysis						
Pus cells (UTI)	Mean± SD	8.93± 4.85	6.81± 3.14	ZMWU = 1.881	0.060	NS
	Median	7.75	6.0			
	Range	5- 22	4-20			
US						
Gestational age by US (weeks)	Mean± SD	8± 1.21	8± 1.53	ZMWU = 1.719	0.086	NS
	Median	8	7			
	Range	6.57- 10.0	6.57- 10.0			
Presence of hematoma	Absent	40 100.0%	38 95%	X^2= 0.513	0.494	NS
	Present	0 0.0%	2 5%			

There was no substantial variations between the studied groups as regards laboratory results and imaging criteria p>0.05. (Table 2)

Table (3): Comparison between the two groups regarding CA-125 level at first visit.

		Group (A) Control group (N=40)	Group (B) Threatened abortion group (N=40)	Test value	P-value	Sig.
CA-125 (IU/ml)	Mean± SD	31.16± 11.05	45.54± 17.09	ZMWU = 5.355	<0.001	HS
	Median	31.12	41.73			
	Range	10.07- 68.0	4.20- 105.0			

There was statistically highly substantial elevation in CA-125 level in threatened abortion group compared to control group p<0.001. (Table 3)

Table (4): Distribution of threatened abortion group regarding different demographics, clinical and radiological data and pregnancy outcome.

	Group (B) Threatened abortion group (N=40)										Test value	P-value	Sig.
	Continued N= 37					Aborted N= 3							
	Mean	± SD	Median	Min.	Max.	Mean	± SD	Median	Min.	Max.			
Age (years)	25.9	5.00	25.00	20.0	35.0	25.7	2.31	27.00	23.0	27.0	25.86	0.794	NS
BMI (Kg/m2)	31.57	2.40	31.49	26.9	35.20	35.15	.	35.15	35.2	35.15	31.57	0.731	NS
Gravidity	1.86	0.86	2.00	1.0	3.00	2.33	1.15	3.00	1.00	3.00	1.86	0.549	NS
History of previous abortion	0.03	0.16	0.00	0.00	1.00	0.67	1.15	0.00	0.00	2.00	.03	1.00	NS
Smoking	7.49	1.52	6.57	6.0	10.0	8.14	1.79	8.00	6.43	10.0	7.49	-	-
Gestational age (weeks)	7.46	1.53	6.60	6.00	10.00	8.13	1.80	8.00	6.40	10.00	7.46	0.063	NS
Hemoglobin (g/dl)	10.87	.53	10.80	9.90	12.10	11.13	.57	11.30	10.50	11.60	10.87	0.808	NS
WBCs (g/dl)	8.05	1.23	7.99	4.50	10.80	7.61	.71	7.61	7.11	8.11	8.05	0.081	NS
Platelets count (g/dl)	237.3	32.02	241.5	178	300	216	19.8	216.00	202	230	237.28	0.373	NS
Pus cells (UTI)	5.89	3.20	4.00	.00	14.00	5.00	1.73	6.00	3.00	6.00	5.89	0.060	NS
Gestational	7.86	3.26	6.00	1.00	16.00	7.00	1.73	8.00	5.00	8.00	7.86	0.086	NS

	Group (B) Threatened abortion group (N=40)										Test value	P-value	Sig.
age by US (weeks)													
CA125	41.53	9.39	41.26	4.20	57.72	95.0	11.80	98.01	81.98	105.0	2.85	0.004	HS
Duration of bleeding	>3 days	3 (8.1%)				3 (100%)					12.9	0.002	HS
Presence of hematoma	Yes	0 (0.0%)				2 (66.7%)					26.7	<0.001	HS

CA125 level was substantially higher in aborted group compared to cases who continued pregnancy p=0.004. (Table 4)

Table (5): Assessment of CA-125 levels in first visit and at follow up (at 14w) in threatened abortion group (who continue pregnancy) n=37

		At first visit	At follow up (at 14w)	Test value	P-value	Sig.
CA-125 (IU/ml)	Mean± SD	45.54± 17.09	41.74± 9.56	Z = 1.682	0.093	NS
	Median	41.73	42.65			
	Range	4.20- 105.0	6.0- 56.90			

There was no substantial variations between CA-125 levels in first visit and at follow up (at 14w) in threatened abortion group (who continue pregnancy) p= 0.093. (Table 5)

Table (6): Relation between CA-125 levels and duration of bleeding in threatened abortion group.

	Bleeding <3 days (n=34)	Bleeding >3 days (n=6)	Mann-Whitney U Test

				Test value	P-value	Sig.
CA-125 At 1st visit	Mean± SD	41.57± 9.69	68.04± 30.71	Z = 1.497	0.134	NS
	Median	41.69	65.05			
	Range	4.20- 57.72	36.98- 105.0			
CA-125 (IU/ml) at 2nd visit	Mean± SD	41.71± 9.87	42.06± 5.98	Z = 0.556	0.616	NS
	Median	42.75	39.64			
	Range	6.0- 56.9	37.67- 48.87			
Presence of hematoma	Absent	38	Present 2	X^2= 11.9	0.001	HS
	Range	4.2-68.4	98.01-105			

P value< 0.05 is significant, p≤0.01 is highly statistically significant

By using ROC-curve analysis, serum CA-125 level can significantly determine patients with threatened abortion with sensitivity and specificity was 77.5% and 79.5% when the cutoff point was >35.12 IU/ml. (Table 6)

Table (7): Validity (Cutoff, Specificity and sensitivity) of serum CA-125 level in prediction of threatened abortion (regard both group) n=80

Variable	Cutoff	Sensitivity	Specificity	PPV	NPV	AUC	95%CI of AUC	P-value
CA-125	>35.12 IU/ml	87.5%	77.5%	79.5%	86%	0.848	0.750 - 0.918	<0.001 (HS)

P value< 0.05 is significant, PPV= Positive Predictive Value, NPV= Negative Predictive Value, AUC= Area under Curve

Cases with subchorionic hematoma had statistically significant elevation in CA-125 at first visit compared to cases without subchorionic hematoma p<0.001. (Table 7)

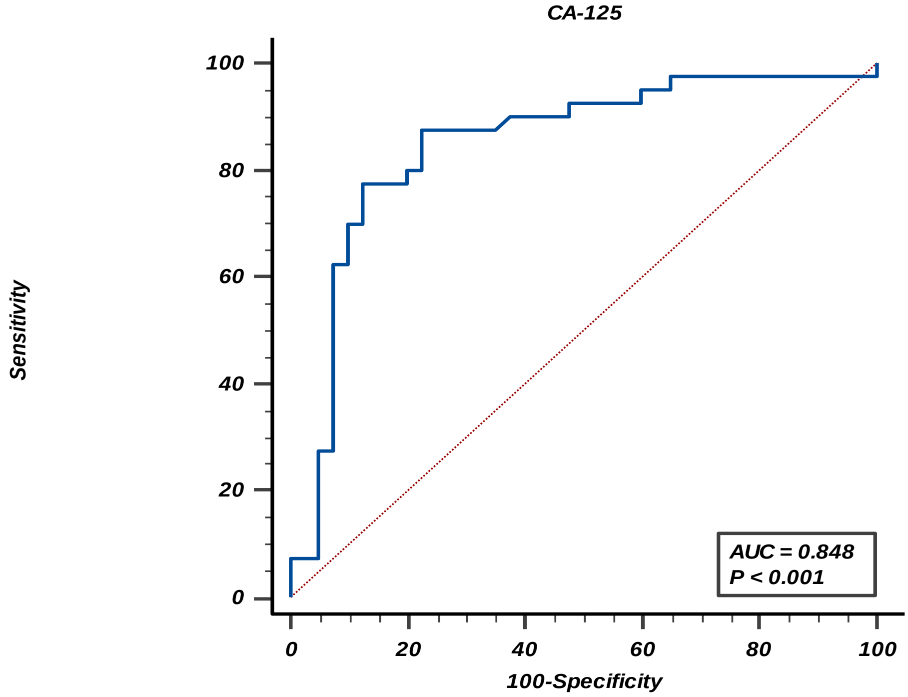

Figure (1): ROC curve for the performance of serum CA-125 level in diagnosis of threatened abortion.

By using ROC-curve analysis, serum CA-125 level can significantly determine patients with threatened abortion with sensitivity and specificity was 77.5% and 79.5% when the cutoff point was >35.12 IU/ml. (Figure 1)

Table (8): Comparison between the two groups regarding the determined cutoff of CA-125.

Variable		Group (A) Control group (N=40)		Group (B) Threatened abortion group (N=40)		Test value	P-value	Sig.
		No.	%	No.	%			
CA-125	<35.12	31	77.5%	5	12.5%	X2= 34.1	<0.001	HS
	>35.12	9	22.5%	35	87.5%			

p≤0.01 is highly statistically significant, X2= Chi- Square test

There was statistically substantial variations between control group and threatened abortion group as regards CA-125 as most cases (87.5%) in threatened abortion group had higher CA-125 >35.12 compared to control group p<0.001.

Discussion

When a woman under 20 weeks gestation has vaginal spotting or bleeding, a closed cervical os, and maybe a modest uterine contraction with an accompanying ultrasound scan that confirms fetal cardiovascular activity, the phrase "threatened abortion" is used in the medical community. (5).

During pregnancy, decidual production and/or release control the levels of CA-125. High amounts of CA-125 were found in the symptomatic patients who aborted, which was caused by the mechanical rupture of the decidua at the moment of impending abortion, which releases the antigen into the mother's bloodstream. (6).

In our study there was statistically highly substantial elevation in CA-125 level in threatened abortion group compared to control group (p value<0.001).

In our study there wasno a statistical substantial variations between control group and threatened abortion group as regards age, BMI, gravidity,history of previous abortion and gestational age.

Our findings are consistent with a prior research conducted by Turgut et al., who reported that there was no a statistical significance between groups regarding hemoglobin, WBCs and platelets count (p value >0.05) (7).

Contrarily, study by Shao et al. who examined the platelet counts of 170 pregnant women with a straightforward pregnancy and 99 women who miscarried between 5 and 10 weeks of gestation. They discovered that pregnant women who had miscarriages had far higher platelet counts than pregnant women who were carrying healthy babies, and that a high platelet count was independently linked to a greater chance of miscarriage. (8).

Our results supported that Mathur et al., who reported that Comparing the threatened abortion group to the normal pregnancy group, there was a substantial increase in serum CA-125. Furthermore, it was much greater among women who went on to miscarry than in those who were able to carry their pregnancy to term (58.04±12.56 versus 19.37±5.7). (p-value less than 0.001) (9).

In the present research, there were no statistically substantial variations between women who aborted and continued pregnancy in threatened abortion group as regarding demographics, personal characteristics and laboratory parameter. There was higher increase in CA125 level in cases with sub chorionic hematoma than cases without sub chorionic hematoma.

A study by Oun et al., reported that regarding previous abortion, 82.7% of studied females had no previous abortion, 13.6% had previous one abortion and, 3.6% had two previous abortions and there was no substantial variations between groups (A) and (B) (p value>0.05). 40.0% reported pain, and there was statistically substantial reduction of pain in group (A) when compared to group (B) (33.7% vs 62.5% respectively) (p value<0.05) (10).

Additionally, study by Turgut et al., revealed that there was no a statistical significance between groups regarding history of previous abortion (p value>0.05) (7).

There was no statistical substantial variations regarding CA-125 level at first visit between patient with bleeding <3 days and cases with bleeding >3 days. Also, the same results at second visit after exclusion of aborted patient (n=3). However, CA125 was high significant difference in patient who have sub chorionic hematoma than patient who not have sub chorionic hematoma.

In line with our finding, Maged et al., When comparing the group with the hemorrhage to the group without, CA125 was significantly greater in the group with the hematoma. (11).

Our results are consistent with a prior research by Oun et al., which found that 7.3% of the female participants in the study had hematomas, and that group (A) had significantly fewer hematomas than group (B) (2.3% vs. 25.0%, respectively). (p-value less than 0.05) (10).

By using ROC-curve analysis, serum CA-125 level can significantly determine patients with threatened abortion with sensitivity and specificity was 77.5% and 79.5% when the cutoff point was >35.12 IU/ml.

The majority of patients (87.5%) in the threatened abortion group had greater CA-125 >35.12 compared to the control group, indicating statistically substantial variations between the two groups in our present research.

Additionally, study by Sudha & Sinha who reported that Using the ROC graphs, the cut-off level of 60 IU/ml was shown to be effective in predicting the likelihood of abortion, with 84.65% sensitivity, 91.87% specificity, 82.53% PPV, 91.11 NPV, and 88.88 accuracy. Consequently, CA 125 has clinical significance in determining the prognosis of individuals facing early-stage pregnancy threats of abortion. (12).

When compare between two groups regarding the determined cutoff of CA-125. In threatened abortion group had higher CA-125 >35.12 compared to control group.

Our results supported with Turgut et al., who reported that by using ROC-curve analysis, serum CA-125 level was (62.6% sensitivity, 62% specificity) for miscarriage (7).

The strengths the study

One of the study's strengths was that the demographic and personal features of the two groups were the same. Expert ultrasonographers had established the adnexal status of every subject, and those with other potential reasons for elevated serum CA-125 were not included in the research. Consequently, the findings showed CA-125 levels from typical expectant mothers. There were no other potential reasons for the CA125 rise.

Limitations the study

Our study's primary flaw was the lack of long-term follow-up to guarantee that there were no instances of preterm delivery or second trimester abortions. Because there were a lot of cases of dropout after the first trimester, statistical analysis was useless beyond that point. If a patient had symptoms that may indicate a miscarriage, the ideal test would be able to predict the fate of the pregnancy from a single serum sample. Since the primary goal of adding biochemical parameter estimate in patients experiencing early pregnancy bleeding is to detect failed gestation and then correlate therapy.

Implications of our results on clinical practice

The use of serum CA-125 levels as a potential predictor of the outcome of threatened abortion could provide clinicians with an additional tool to identify pregnancies at increased risk of miscarriage or other adverse outcomes. This could help guide clinical decision-making and improve patient care.Serum CA-125 levels are a reliable predictor of pregnancy outcome, they could be incorporated into routine clinical practice as a standard part of the diagnostic workup for women with threatened abortion. This could help identify women who may benefit from more aggressive management or closer monitoring, such as those at high risk of miscarriage or preterm birth.

Implicationsfor future research

Future research in the field of threatened abortion should aim to further investigate the role of serum CA-125 as a potential predictor of pregnancy outcomes. This could involve large-scale, well-designed prospective studies that evaluate the association between serum CA-125 values and the risk of miscarriage and there is a causal association or not as well as other adverse pregnancy outcomes.Long duration monitoring & follow up & if CA125 level can predict the of going pregnancy from failed pregnancy.

Conclusion

Serum CA125 is a valid and reliable predictor of pregnancy outcome in patient with threatened abortion, the levels are correlated to US finding, it has a sensitivity 77.5 & specificity 79.5 when cutoff point was >35.12 IU/ml.

Recommendations

In situations when abortion is imminent, CA125 levels are higher; the cutoff limit was >35.12 IU/ml. This is a very sensitive prognostic indicator that is also rather inexpensive to test in a poor country like Egypt. This will allow the supervising physician advise the women and their partners and aid in the treatment of impending miscarriages as well as in predicting the potential fate of the pregnancy. More research with a bigger sample size is required to validate the present findings.

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