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Role of CA-125 and Ultrasound in Prediction of outcome of Threatened Abortion

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ABSTRACT

Background: The term "threatened abortion" refers to a clinically descriptive condition in which women who are less than 20 weeks pregnant experience cervical closure, vaginal spotting or bleeding, and maybe moderate uterine cramping. Ultrasonography and maternal serum cancer antigen-125 (CA-125) appear to be useful biomarkers for early pregnancy outcome prediction in cases of impending miscarriage.

Objectives: This work aimed to study the role of serum CA-125 and Ultrasound in early prediction of outcome of threatened abortion.

Patients and methods: This case control study was conducted in El- Menoufia University Hospital and El- Warak General Hospital from February 2021 to March 2022. Full history taking, obstetric history, menstrual history, ultrasonography, and serum CA-125 measurements were done for all studied women.

Results: Significant area under curve with cutoff > 29 IU/ml showed that CA-125 had a very high reliability of differentiation between the complete abortion group and the control group, aborted cases were highly significant as regards high CA-125 (P=0.000). Multivariate analysis revealed that the most significant predictors of threatened abortion were yolk sac diameter (YSD), followed by CA1-25, with OR (95%), p-value [5.014 (1.985-8.068)], p-value < 0.001; [3.712 (2.056-6.446), p-value 0.027], while the rest had insignificant predictors of threatened abortion, with p-value (p > 0.05).

Conclusions: The use of CA-125 and ultrasound in the first trimester represents a non-invasive, early, and rapid procedure that may be regarded as a good predictor of the outcome of pregnancy in instances with threatening abortion with cut off level more than 29 IU/ML of CA-125.

Keywords: Outcome prediction, Serum CA-125, Threatened abortion, Ultrasonography.

INTRODUCTION

Threatened abortion, which is estimated to occur in one-fifth of pregnancies, is the phrase used to characterize a woman who is less than 20 weeks pregnant, having vaginal bleeding with a closed cervical os, and maybe modest uterine contractions with a live fetus [1].

The high molecular weight glycoprotein known as cancer antigen (CA-125) is found in the ovaries, endometrium, endocervix, and the epithelia of the tubes and amnion. Pregnant women's sera contain CA-125 antigen, which is produced by the decidual cells when trophoblastic cells invade them [2]. Because its levels are elevated in the early stages of pregnancy and right after delivery, which suggests the disintegration of the mother decidua, disruption of the fetal membrane's epithelial basement membrane may potentially cause a rise in the mother's CA-125 level during pregnancy, which may then be used as a predictor of a subsequent spontaneous abortion [3].

Numerous biomarkers, including blood progesterone, HCG, and inhibin A, can be used to predict the outcome of a threatened abortion. However, their usefulness diminishes after fetal viability is confirmed [4]. Low amounts of HCG in women who are facing threats of abortion point to a poor pregnancy outcome [5].

Transvaginal ultrasonography is essential to detect whether the fetus is still alive and to diagnose an incomplete or missed abortion. A pelvic examination will reveal whether the cervix is effaced or dilated, suggesting an impending miscarriage [6].

In determining the initiation and assessment of early pregnancy, ultrasonography (USG) is crucial [7]. The imaging of the gestational sac is the first conclusive sonographic result that suggests an early pregnancy [8].

The measurement of the YSD can be significant during the initial trimester of pregnancy. If the yolk sac is absent or disproportionately big, it may indicate an imminent risk of miscarriage [9]. When embryonic heartbeats are present, a very big yolk sac may exist in a normal pregnancy. However, poor quality and early regression of a yolk sac are more precise indicators of pregnancy loss than huge yolk sac size [10]. The aim of this work was to study the role of serum CA-125 and ultrasound in early prediction of outcome of threatened abortion.

PATIENTS AND METHODS

This case-control study was conducted in El-Menoufia University Hospital and El-Warak general hospital from February 2021 to March 2022.

Sample size estimation: Based on previous study by **Anter *et al.*** [11] who reported that specificity of CA-125 as a predictor of complete abortion was 98.6 %. Minimum total sample size needed for each group is 30 patients according to the following formula: Where; z1-α**:** z score for CI 95% and equals 1.96 Specificity= 0.986 Prev: Prevalence of threatened abortion in early pregnancy= 0.25 d: degree of precision= 0.05.

Inclusion criteria: Sixty women are 6-12 weeks pregnant. Participants in the research were selected based on their last menstrual period (LMP) date and had regular cycles. 30 women were clinically

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identified as threatening abortion (complaints of vaginal bleeding, with or without pelvic pain, and positive fetal life on ultrasonography). The other thirty women were pregnant at 6-12 weeks without vaginal bleeding.

Exclusion criteria: History of blighted ovum, history of molar pregnancy, history of ectopic and high-order pregnancy, ovarian tumors during pregnancy, pelvic endometriosis, and ovarian hyperstimulation.

Complete history, physical, and sonographic examination to establish gestational age (GA) by gestational sac diameter (GSD)-yellow sac diameter-crown rump length), fetal viability and intrauterine single gestation.

The women were divided into two groups: Group (I) included 30 women 6-12 weeks(Calculated by date of LMP, with regular cycles) with threatened miscarriage, identified by vaginal bleeding with or without pelvic pain and positive fetal life by ultrasonography. Group (II) included 30 age-matched women pregnant 6-12 weeks (Calculated by date of LMP, with regular cycles) without vaginal bleeding who were recruited in the study and followed till 20 weeks of pregnancy as the controls.

All women were subjected to:

Obstetric history that included a history of prior full-term births, premature labors, abortions, delivery methods, and fetal outcomes.

Menstrual history: Negele's rule can be used to estimate GA if the woman had regular cycles for the final three months before becoming pregnant.

Past history: History of illnesses, abdominal surgeries, medication use, allergies, and a comprehensive physical examination that included a look at the abdomen, heart, and chest as well as a thorough clinical assessment (blood pressure, temperature, and pulse).

Ultrasonography (Philips clearvue 650a and Chison 8500, USA)**:** To assess gestational sac diameter (GSD), fetal viability, YSD, crown rump length, exclusion of any ovarian or uterine abnormalities, as well as any uterine deformities.

Serum CA-125 measurements: On the day of the ultrasound examination, a 5-milliliter venous blood sample was taken from each patient. The samples were centrifuged, and the serum was stored frozen for later analysis. Maternal serum CA-125 is evaluated only once, at the time of recruitment, as soon as the mother arrives for a reservation. Using the Cobas 410 complete auto-motion test, serum levels of CA-125 were determined. Every sample that was measured was examined. The patient was comforted and told to take physical and mental rest at home in response to the potential miscarriage. Up until 20 weeks, weekly follow-up appointments were scheduled at the outpatient clinic.

Ethical approval: Menoufia Faculty of Medicine Ethics Committee approved this study. After obtaining all of the information, all participants gave their signed approval. The Helsinki Declaration was observed throughout the study's operations.

Statistical Analysis

Using a personal computer running SPSS version 20.0, the following statistics were used after data were gathered, tabulated, and statistically examined. The terms "number (no), percentage (%), arithmetic mean ± SD, and percentage (%) expressed descriptive statistics. Tests for analytical statistics included the Mann-Whitney test, ROC curve, Student t-test, X^2-test, and regression analysis. A significant level is defined as a P value ≤ 0.05.

RESULTS

Regarding demographic data of population under study there is no significant correlation regarding age, BMI, party, and GA between two studied groups. Also, there was no significant difference regarding history of preterm labor, gestational diabetes mellitus (GDM) and HTN between two studied groups (Table 1).

Table (1): Demographic data of the studied women

	Threatened abortion (n=30)	Controls (n=30)	Sig. test	P value
Age(years) Mean± SD	27.1±5.27	25.23±3.7	t=1.587	0.118
BMI (kg/m^2) Mean ± SD	26.5±4.28	24.47±4.09	t=1.881	0.065
Parity Mean ± SD	2.22 ±1.76	1.25 ±1.16	U=2.91	0.004*
GA Median (IQR)	8 (7-9)	7(7-9)	U=433	0.796
History of preterm labor No	28(93.3%)	30(100%)		
Yes	2(6.7%)	0(0%)	FX=2.069	---
Diabetes mellitus No	25(83.4)	29(96.6)		
Yes	5(16.6)	1(3.4)	FX=2.963	---
History of hypertension No	30(100%)	30(100%)	----	

*****significant

Threatened abortion women had a significantly greater mean YSD/mm compared to the control group ($p < 0.001$). There was no significant difference between groups based on scan type, gestational sac shape, or GSD (mm), CRLD (mm) and FHR (b/m) with p-value ($p > 0.05$). Also, threatened abortion women significantly associated with abortion (Table 2).

Table (2): Imaging data and the pregnancy outcomes among the studied women

	Groups							
	Threatened abortion (n=30)		Controls (n=30)		Total		$\chi 2$	P value
	No	%	No	%	No	%		
Type of scan Trans	25	83.4	22	73.4	47	78.4	0.88	
vaginal	5	16.6	8	26.6	13	21.6		0.34
Trans abdominal								
Gestational sac shape								
Irregular	1	3.4	2	6.6	1	1.6	0.35	0.55
Regular	29	96.6	28	93.4	59	98.4		
YSD (mm)	5.54±0.87		4.40±0.67		4.97±0.96		t=5.685	<0.001*
GSD (mm)	29.43±10.42		29.96±13.33		29.69±11.86		t=0.173	0.864
CRLD (mm)	19.16±9.53		17.99±12.59		18.58±11.09		U=0.406	0.686
FHR (b/m)	123.03±18.15		121.53±19.09		122.28±18.48		t=0.312	0.756
Abortion								
No	17	7.56	28	93.3	45	75	X^2=	0.002*
Yes	13	43.3	2	6.7	15	25	756. 10	
Total	30	100	30	100	60	100		

*****significant

Also, the mean level of CA-125 in the threatened abortion women was significantly increased more than in controls (P=0.0001). The YSD was highly significant in predicating abortion **(**Table 3).

Table (3): Serum CA-125 level among the studied women

	Threatened abortion (n=30)	Controls (n=30)	Test of significance	P-value
CA 125 Median (IQR)	31(24.33-33.5)	13.8(12-16.25)	U=69	0.0001*
YSD /mm Mean ±SD	5.47±79	4.05±0.54	t= 11.37	0.001*
CA-125	2(6.6%)	29 (96.6%)	X^2	
<29 IU/ML	28 (93.4%)	1(3.4%)	=48.65	0.0001*
>29 IU/ML				

Additionally, YSD significantly higher among aborted women (5.51 ± 68) than in without abortion (4.12 ± 29) (P=0.0001). In this concern, aborted cases were highly significant as regards high CA-125 (34.533 (32-36) compared without abortion (16 (13-22.15), (P=0.0001) (Table 4).

Table (4): Relation between ultrasound findings and abortion in threatened abortion women

	Abortion			
	Yes (N=13)	No (N=17)	U	P
GSD (mm) Mean ± SD	51.92±11	56.092±10.07	0.37	0.71
YSD Mean ± SD (mm)	5.51±68	4.12±29	t= 11.57	0.0001*
Crown rump length (mm) Mean ± SD	31.42±15.97	36.92±21.22	0.84	0.644
CA-125 Median (IQR)	34.533 (32-36)	16 (13-22.15)	43.5	0.0001*

*****Significant

Regarding the validity of CA-125 as predictor of complete abortion, a significant area under curve with cut off of > 29 IU/ml, showed that CA-125 has a very high reliability of differentiation between the complete abortion group and the control group with sensitivity of 86.7%, specificity of 83.3% and accuracy of 86.67% (Table 5).

Table (5): Validity of CA 125 as predictor of complete abortion

Area under curve	Cut off point	P	Sensitivity	specificity	PPV	NPV	Accuracy	Confidence interval	
								Lower	upper
0.936	>29IU/ML	0.0001*	86.7%	83.3	95.12%	68.42%	86.67%	0.875	0.996

Multivariate analysis revealed that the most significant predictors of threatened abortion were YSD, followed by CA-125, with OR (95%), p-value [5.014 (1.985-8.068)], p-value <0.001; [3.712 (2.056-6.446), p-value 0.027]; while the rest had insignificant predictors of threatened abortion, (p > 0.05) (Table 6).

Table (6): Multivariate logistic regression analysis for factors predictors for threatened abortion.

	β	**Wald**	**Sig.**	**OR**	**95% C.I.**
					LowerUpper
GA	0.247	1.362	0.162	1.682	1.1052.748
CA-125	1.994	5.736	0.027*	3.712	2.0566.446
GSD	0.349	0.654	0.821	1.092	0.1042.972
YSD	2.254	8.349	<0.001**	5.014	1.9858.068
FHR	0.225	1.513	0.398	1.598	1.1402.582
Crown rump length	0.177	0.913	0.374	1.362	0.9722.147

β: Regression coefficient, OR: Odd ratio, CI: Confidence interval, *Significant.

DISCUSSION

In the present study among the 30 patients who presented with threatened miscarriage (group I) 17 of 30 (56.7%) continued their pregnancy and 13 0f 30 (43.3%) had miscarried, and among control group (group II) 28 of 30 (93.3 %) continued their pregnancy and 2 of 30 (6.7 %) had miscarried. These results were matching with **Han and Tan** [12] it found that, at any point throughout their pregnancy, 55.3% of women who had a threatened miscarriage in the first trimester went on to have a full miscarriage [13]. In contrast to our research, **Chitra *et al.*** [14] documented that 60 participants in his study complained of vaginal bleeding during the first trimester of pregnancy. When the results were analyzed at 20 weeks of pregnancy, 42 (70%) of the 60 individuals had their pregnancies completed, whereas 18 of the 30 (%) terminated in abortions.

Sudh *et al.* [15] stated that in their research of 100 pregnant women who complained of early pregnancy vaginal bleeding, the result of the pregnancy at 20 weeks was 32 of 100 (32%) aborted during follow-up and 68 (68%) continued the pregnancy. **Anter *et al.*** [11] observed that in their research of 80 pregnant women, 9 of 40 from the endangered group (22.5%) miscarried. According to **Mansy *et al.*** [16], 15 instances (16.6%) out of the 90 pregnancies ended in abortion. According to **Abd EL-rauof *et al.*** [17], out if 139 women who were threatened with miscarriage, 36 (or 25.9%) of them underwent a full abortion.

In our investigation, we discovered that the YSD in the endangered group is really significant, and associated with increased serum level of CA-125 [31(24.33-33.5). This is consistent with **Radwan *et al.*** [18] finding that instances of threatened abortion had YSDs that were much greater. Additionally, our research supports the findings of **Anther *et al.*** [11], who found a significant correlation between abnormal YSD (> 6) and miscarriage. **Hanaa *et al.*** [19] also found a significant correlation between abnormal YSD (< 3 or > 6) and miscarriage. Also, our research supports the findings of **Xie *et al.*** [20], who found a strong correlation between miscarriage and an aberrant YSD (> 6). Our findings contradict those of **Maged and Al-Mostafa** [21], who claimed that the crown rump length (CRL) is a reliable ultrasonographic marker for predicting the outcome in women who are facing an abortion danger. **Reljic** [22] examined 310 singleton pregnancies in which the fetus was alive and the mother had threatened to miscarry before the baby was 13 weeks gestation. They found that the incidence of a later spontaneous miscarriage was significantly positively correlated with a deficiency in the CRL for gestation in fetuses with CRL < 18 mm. This disparity could be explained by the lower sample size of women in our research.

On current study, the mean diameter of the gestational sac at 28–42 days from the LMP among normal pregnancies did not differ significantly from that of those who later miscarried (2.6 vs. 2.7 mm), as reported by **Oh *et al.*** [23]. This finding is consistent with the observation that there was no significant difference in GSD between the two studied groups. Our findings contradict those of **AL Mohamady *et al.*** [24], who found that the miscarried group's mean GSD was considerably lower than that of the

continuing group (P=0.023). **Falco *et al.* [25]** assessed the prognostic factors and result of pregnancies with a gestational sac ≤ 16 mm and first-trimester hemorrhage. They discovered that 32 (64%) of the 50 patients experienced miscarriage where the size of GSD had a high degree of statistical significance, and these findings did not agree with ours.

Fetal heart rate did not differ statistically significantly between the two groups in the current investigation, which is consistent with the findings of **Doubilet and Benson [26]**.

Our findings concur with those of **Anther *et al.* [11]**. As in another study by **Tannirandorn *et al.* [27]**, the result is still unknown when the fetal heart rate is within the usual range for gestation.

In the current investigation, we discovered a statistically significant rise in CA-125 in individuals who had an abortion compared to those who carried on with their pregnancy past 20 weeks (43.533 ± 32-36 versus 16 ± 13- 22.15). Furthermore, at a threshold value > 29IU/ml, the sensitivity of CA-125 in predicting abortion in the females under study was 86.7%, while the specificity was 83.3%.

Similar to our research, **Abd-Elrauof *et al.* [17]** discovered a statistically significant rise in CA-125 in individuals who had an abortion compared to those who carried on with their pregnancy over 24 weeks (53.83 ± 9.48 vs. 19.45 ± 5.57 respectively). Furthermore, at a threshold value of > 35 IU/ml, the sensitivity of CA-125 in predicting abortion in the female subjects under study was 100.0%, while the specificity was 98.8%.

In agreement with **Ayaty *et al.* [28]** findings, the mean level of CA-125 in patients who were ultimately aborted was 58.17±7.25 IU/mL, while it was 26.61±1.76 IU/mL in healthy pregnant women who carried their pregnancy to term. Threatened women who carried their pregnancy to term without aborting it had a CA-125 level of 30.89 IU/ml. They came to the conclusion that serum CA-125 testing could be a cheap, accessible, sensitive, and specific indicator of the outcome of a threatened abortion that ends in fetal loss. Our findings concur with the researches of **Al Mohamady *et al.* [24], Yu *et al.* [29]** and **Madendag *et al.* [30]**. While, **Mahdi [31]** found no statistically significant difference in the amount of CA-125 between patients who miscarried and those who completed their pregnancies despite the increased level, there was a highly significant rise in the level of this protein in the blood in women who miscarried.

CONCLUSIONS

The use of CA-125 and Ultrasound in the first trimester represents a non-invasive, early, and rapid approach that can be regarded as a good predictor of pregnancy outcome in cases of threatened abortion with a CA-125 cut-off level more than 29 IU/ML.

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