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Full Length Research Paper

Role of Both Serum CA125 and Ultrasound in Prediction of Pregnancy Outcome in First trimester Threatened Miscarriage

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Abstract
Threatened abortion is a clinical dilemma for the obstetrician regarding the outcome of pregnancy. Threatened abortion is a clinically descriptive term applied to women who are less than 24 weeks of gestation having vaginal spotting or bleeding, closed cervical os and possibly mild uterine cramps. It may progress to a term viable pregnancy or may result in incomplete, complete, missed or septic abortion. Threatened abortion is the most common complication of pregnancy in the first half of gestation. Threatened abortion is such an event during pregnancy, which needs meticulous attention to fulfill the purpose of healthy baby from healthy mother. It occurs in about 20% of early pregnancies.3 Most of these pregnancies continue to term with or without treatment. Spontaneous abortion occurs in less than 30% of the women who experience threatened abortion. The aim of this study was to determine the role of both serum CA125 and ultrasound in prediction of pregnancy outcome in first trimester threatened miscarriage. This study included 110 women attended to outpatient clinic of obstetrics and gynecology department, Al-Azhar University hospital (New Damietta) with manifestations of first trimester threatened miscarriage. CA125 represents 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.

Keywords: *CA125, Threatened miscarriage, ultrasound in prediction of pregnancy outcome.*

Introduction

Threatened abortion is a clinical dilemma for the obstetrician regarding the outcome of pregnancy. Threatened abortion is a clinically descriptive term applied to women who are less than 24 weeks of gestation having vaginal spotting or bleeding, closed cervical and possibly mild uterine cramps. It may progress to a term viable pregnancy or may result in incomplete, complete, missed or septic abortion *(Cunningham et al., 2014).*Ultrasonography, serial serum quantitative assessment of β-subunit of human chorionic gonadotropins (β-hCG), serum cancer antigen -125 (CA-125) and serum progesterone values measured alone or in various combinations, have proven helpful in ascertaining if a live intrauterine pregnancy is present. Maternal serum biochemistry has also been proposed as a predictor. *Korevaar et al. (2017)* reported that the presence of low concentrations of hCG in women with threatened abortion suggests a negative outcome for the pregnancy. A thorough evaluation is therefore essential to establish the diagnosis. Initial laboratory tests should include a complete blood count and blood typing. A pelvic examination will determine whether the cervix is effaced or dilated, indicating imminent miscarriage. Finally, transvaginal ultrasound is crucial to confirm whether the fetus is still viable, and to diagnose an incomplete or missed abortion *(Datta and Raut, 2017).* The purposes of this study is to determine the role of both serum CA125 and ultrasound in prediction of pregnancy outcome in first trimester threatened miscarriage

Patient and methods

This study included 110 women attended to outpatient clinic of obstetrics and gynecology department, Al-Azhar University hospital (New Damietta) with manifestations of first trimesterthreatened miscarriage.

Study design: Prospective clinical comparative study.

Inclusion criteria: Maternal age (20-35 years), Gestational age (7-13 weeks),patients in their first trimester of a singleton spontaneous pregnancy presenting with vaginal bleeding or spotting and A visible gestational sac of a living embryo, verified by cardiac activity

Exclusion criteria: History of general medical disease e.g. diabetes or thyroid disease, presence of local (gynecological) disease e.g. fibroid or adnexal masses verified by normal appearance of the uterus and ovaries by ultrasound,Patients with history of

recurrent miscarriages, Presence of uterine malformation as septate uterus.History of any maternal disease that would cause an increase in CA-125 level such as chronic pelvic infection and endometriosis.All females in the study will subjected to Verbal consent, detailed clinical history, Personal history (Age, residence, race and occupation), Present history (onset, course and duration of vaginal bleeding), Obstetric history (parity& obstetric complication), Menstrual history, past and family history.

- Clinical examination: General examination, local examination .to asses' state of cervix and vaginal bleeding.
- Ultrasound: viability, gestational age, ascertain that closed cx, exclusion of uterine malformation and uterine lesions.
- Investigation: Evaluation of maternalserum ca125through obtaining 5ml of venous blood from each patient on the same day of u/s examination

Follow-up schedule

Follow up of pt. will be carried out until 24 weeks and patientswill besubdivided into 2groups
Group (A): will continue their pregnancy
Group (B): will abort
Thencomparison between two groups are done as regard ultrasonography and serum CA 125.

Statistical analysis of data

The collected data were presented as mean and standard deviation, minimum and maximum for numerical variables; while qualitative variables were presented as frequency and percent. Comparison between groups was done by independent samples (t) test for numerical variables and Chi square (X2) or Mann-Whitney (U) test. Correlation between variables was estimated by bivariate Pearson's correlation coefficient (r), while sensitivity and specificity and best cutoff values were calculated through receiver operation characteristics (ROC) curve. P value < 0.05 was considered significant. All statistical analysis was done by Statistical Package for social science (SPSS) version 18 (SPSS®, Inc., Chicago, Illinois, USA), and MedCalc Statistical Software version 15.8 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2015)

Results

This study included 110 women attended to outpatient clinic of obstetrics and gynecology department, Al-Azhar University hospital (New Damietta) with manifestations of first trimesterthreatened miscarriage. Regarding to the incidence of abortion 24 of them (21.8%) already had abortion before 24 weeks gestation; while 86 females (78.2%) continued their pregnancy after the 24 week of gestation. (Table 1). Regarding patient age, it ranged from 20 to 35 years; and there was no significant difference between groups (A) and (B) (25.96±2.14 vs 26.75±2.98 years respectively). Regarding gravidity, it ranged from 1 to 4, and there was no significant difference between groups (A) and (B). Regarding parity, it ranged from 0 to 3 and there was no significant difference between groups (A) and (B) (Table 2). 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 significant difference between groups (A) and (B) (Table 3). In the present work, 40.0% reported pain, and there was statistically significant decrease of pain in group (A) when compared to group (B)(33.7% vs 62.5% respectively). In addition, hematoma was reported in 7.3% of studied females and there was significant decrease of hematoma in group (A) when compared to group (B) (2.3% vs 25.0% respectively (Table 4). As regard to ultrasonography gestational age, it ranged from 7 to 13 weeks, and there was statistically non-significant difference between groups (A) and (B) (9.41±1.33 vs 9.58±1.47 respectively. And crown rump length, it ranged from 0.60 to 6.90 cm, and there was no significant difference between group (A) and (B) (2.72±0.68 vs 2.49±0.76 respectively). On the other hand, gestational sac diameter ranged from 2.20 to 6.50 cm, and there was statistically significant increase in group (A) when compared to group (B) (3.57±0.49 vs 3.10±0.27 cm respectively) (Table 5). As regard to CA125 levels, it 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). (Table 6).As regard to sensitivity of different studied variable in prediction of threatened abortion, the best was CA125, with a sensitivity of 1000% and specificity of 98.8% at cutoff value > 35 IU/ml; followed by fetal heart rate, with sensitivity of 100.0% and specificity of 95.3% at a cutoff value ≤ 140 beat/minute. Then gestational sac diameter, with sensitivity of 75% and specificity of 83.7% at a cutoff value ≤ 3.2cm; and finally, CRL with sensitivity of 75% and specificity of 47.7%, at a cutoff value ≤ 2.6cm (Table 6).

Table (1): Incidence of threatened abortion in studied populations

	n	%
Group A (continued)	86	78.2
Group B (Aborted)	24	21.8
Total	110	100.0

Table (2): Comparison between studied groups as regard patient age

	Mean	SD	Minimum	Maximum	t	P
Group A (continue)	25.96	2.14	20.00	33.00		
Group B (Aborted)	26.75	2.98	22.00	35.00	1.44	0.15

Total	26.13	2.36	20.00	35.00		

Table (3): Comparison between studied groups as regard gravidity

		Group				Total	
		Group A (continue)		Group B (Aborted)			
		n	%	n	%	n	%
Gravidity	1.00	16	18.6%	6	25.0%	22	20.0%
	2.00	20	23.3%	8	33.3%	28	25.5%
	3.00	28	32.6%	7	29.2%	35	31.8%
	4.00	22	25.6%	3	12.5%	25	22.7%
Statistics		χ^2= 2.61 , p = 0.45					

Table (4): Comparison between studied groups as regard parity

		Group				Total	
		Group A (continue)		Group B (Aborted)			
		n	%	n	%	n	%
Parity	0.00	16	18.6%	6	25.0%	22	20.0%
	1.00	26	30.2%	9	37.5%	35	31.8%
	2.00	30	34.9%	7	29.2%	37	33.6%
	3.00	14	16.3%	2	8.3%	16	14.5%
Statistics		χ2 = 1.69 , p = 0.63					

Table (5): Comparison between studied groups as regard pain, sub-chronic hematoma

		Group				Total		χ^2	p
		Group A (continued)		Group B (Aborted)					
		N	%	n	%	n	%		
Pain	Yes	29	33.7%	15	62.5%	44	40.0%	**6.47**	**0.011***
	No	57	66.3%	9	37.5%	66	60.0%		
Hematoma	Yes	2	2.3%	6	25.0%	8	7.3%	**14.30**	**0.001***
	No	84	97.7%	18	75.0%	102	92.7%		

Table (6): Comparison between studied groups as regard CA125 (IU/ml)

	Mean	SD	Minimum	Maximum	t	p
Group A (continued)	19.45	5.57	8.00	44.00	**22.55**	**<0.001***
Group B (Aborted)	53.83	9.48	39.00	77.00		
Total	26.95	15.70	8.00	77.00		

Table (7): Sensitivity, specificity of ultrasound parameters, and CA125 in prediction of threatened abortion

	AUC	Cutoff	Sensitivity	Specificity
CA125	0.98	>35	100.0%	98.8%
CRL	0.59	≤2.6	75.0%	47.7%
GSD	0.84	≤ 3.2	75.0%	83.7%
Fetal HR	0.95	≤ 140	100.0%	95.3%

Discussion

Pregnancy loss is a common medical problem in reproductive-aged females, with around 25% of all women attempting pregnancy experiencing at least one spontaneous abortion. Medically, all pregnancy losses before 20 weeks' gestation termed as abortion (Sedgh et al., 2012; Steinberg, 2011). More than fifty percent of human pregnancies are aborted before term. The majority are unrecognized occurring before or with the expected next menses. About 10–12% of all clinically diagnosed pregnancies are lost as first-trimester or early second trimester. The rate of fetal death after 14 weeks' gestation is much lower than the rate of pre-embryonic and embryonic loss (Kolte et al., 2015). Sporadic abortion is the commonest adverse outcome inhuman reproduction. In the majority of sporadic spontaneous abortions, an etiology is unknown. A spontaneous abortions or miscarriages were expected to occur in 15–25% of all pregnancies (Marwan et al., 2012). CA125 (cancer antigen 125 or carbohydrate antigen 125) also known as mucin 16 or MUC16. MUC16 is a member of the mucin family glycoproteins. CA125 has found application as a tumor marker or biomarker that its level may be increased in the serum of some patients with specific types of cancers, or other benign conditions (Felder et al., 2014).

There are two theories explaining the rise of maternal serum CA125 in the first trimester. The most accepted one is the tubal reflux theory of Quirk et al. According to this theory, CA125 with decidual origin passes to maternal compartment via tubal reflux

and rises in the circulation after the absorption by peritoneal lymphatics. As the pregnancy proceeds, a functional obstruction occurs due to the fusion of decidua scapsularis and deciduasparietalis in tuba uterine, and serum CA125 levels decrease (Menczer et al., 2015).

The second theory is explained as the crossing of CA125 to the maternal blood circulation due to damage in decidual cells occurred by chorionic villus invasion in early pregnancy and by placental separation at birth (Bon et al., 2001). Some studies detected that the abortion risk is increased in pregnant women with higher CA125 levels.The present study was designed as a prospective study to evaluate the role of CA125 a biochemical markers, and ultrasound parameters (Crown rump length, Gestational sac diameter and fetal heart rate) in prediction of abortion in patients with threatened abortion. It included 110 females who presented by vaginal bleeding with closed cervix at gestational age of 7 to 13 weeks. They were underwent full history taking, clinical examination, laboratory and ultrasound investigations. In the present study, there was no statistically significant difference between studied groups as regard to age, gravidity, parity, number previous abortions or gestational age. These results are comparable to those reported by Maged and Al-Mostafa (2013) who reported that, there was no significant difference between the three study groups regarding age, parity, BMI, gestational age at study or number of previous abortions. In addition, Al Mohamady et al. (2016) reported that, no statistically significant differences were found between both groups as regards maternal age, parity or the number of previous miscarriages. In the present work, the incidence of abortion before 24 weeks of gestation was 21.8%, and this is comparable to the value of 20% reported by Al Mohamady et al. (2016),and this is higher than that reported by Mansy et al. (2017) who reported that, Out of the 90 pregnancies, 15 cases (16.6%) had aborted during follow-up. The possible explanation for higher rate of abortion in the present work when compared to their study is that, they included all pregnant females with singleton pregnancy, while we included only females with threatened abortion. On the other hand, results of the present work are comparable to those reported by Kouk et al. (2013) who reported that, 36 (25.9%) of the 139 women who experienced a threatened miscarriage progressed to a complete miscarriage within 16 weeks of gestation. Other studies reported percentages around this value (Basama and Crosfill, 2004; El-Zibdeh and Yousef, 2009; Omar et al., 2005). However, the percentage of the complete threatened abortion in the present study is much lower than that of the 1992 study conducted in Singapore, which reported that 55.3% of women who experienced a threatened miscarriage in the first trimester progressed to a complete miscarriage at any time during their pregnancy (Han and Tan, 1992). The shorter follow up duration in the present work, and possibly improvements in the management of threatened miscarriage over the years, may account for this discrepancy.

In contrast, other studies have reported that less than 10% of women who experienced a threatened miscarriage progress to a complete miscarriage (Johns et al., 2003; Johns and Jauniaux, 2006). However, these studies – like us - included women with a viable fetus on ultra-sonographic examination, which accounts for the low rate of progression to a complete miscarriage. In the present work, we found statistically significant increase of CA125 in aborted patients when compared to patients that continued their pregnancy after 24 weeks (53.83±9.48 vs 19.45±5.57 respectively). In addition, the sensitivity of CA125 in prediction of abortion in studied females was 100.0% and specificity was 98.8% at a cutoff value of > 35 IU/ml. These results are in agreement with Ayaty et al. (2007)who in their study compared 50 women with healthy pregnancy and 50 women with threatened abortion of the level of CA 125 and followed up the outcome. The mean level of CA-125 in finally aborted patients was 58.17±7.25 IU/mL and in normal pregnant women, who continue to term, was 26.61±1.76 IU/mL. The CA-125 level in threatened women, whose pregnancy continued and did not abort, was 30.89 IU/ml. They concluded that measurement of serum CA-125 may be an inexpensive, easily available, sensitive and specific predictor of outcome in threatened abortion, which results the loss of pregnancy.

In addition, Maged and Al-Mostafa (2013)in their study reported that, CA125, Beta hCG and progesterone are good biochemical markers for the prediction of outcome in women with threatened abortion. This study involving 250 women in their first trimester who were divided into three groups: group I (65 women) in whom threatened abortion ended in abortion, group II (85 women) with threatened abortion who completed their pregnancy and group III (100 women) with normal pregnancy. There was a statistically significant difference between group 1 and the other 2 groups regarding CA 125. The sensitivity, specificity of CA 125 at 80 IU/mL was 80.2% and 78.3%, respectively. In agreement with the results of the present work, (Al Mohamady et al. (2016) 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 Scarpellini et al. (1995) who studied 52 women with non-threatened pregnancies versus 48 with threatened abortions. They found that women with threatened pregnancies had statistically significantly higher CA 125 than non-threatened pregnancies, especially those with a negative outcome (P < 0.01). The CA 125 and β-hCG association showed a higher prognostic value (sensitivity 78.9·, specificity 96.5%) in assessing pregnancy outcome than CA 125 or β-hCG alone (sensitivity 78.9% and 57.9%, respectively; specificity 75.8% and 86.20%, respectively). The lower sensitivity in their work when compared to the present study can be attributed to different inclusion criteria, as only females with threatened abortions were included in the present study. On the other hand, these results are in contradiction to the study by Mahdi et al. (2009), who in their study for estimation of CA-125 Level in first trimester threatened abortion concluded that CA-125 cannot be used as a predictor of outcome of early pregnancy complicated by vaginal bleeding. This may be due to the small number of patients in their study. In addition, Hornstein et al. (1995) studied 188 pregnant patients who had weekly serum CA 125 levels obtained after a prepregnancy baseline

value was determined. There was no statistically significant difference in the CA 125 levels of patients who aborted compared with those of women whose pregnancies continued. In addition, among patients with CA 125 values >150 U/ml there was also no statistically significant difference in the proportion of patients who aborted compared with controls. They concluded that serum CA 125 levels are not predictive of spontaneous abortion in the first trimester of pregnancy.Several cut-off values were suggested in other studies in order to predict pregnancy outcome in early viable pregnancies complicated by vaginal bleeding or to discriminate between viable and non-viable gestations at the time of vaginal bleeding. In this study, a cut-off limit of 35 IU/ml of CA-125 level was suggested, with a sensitivity of 100.0% and specificity of 98.8%.

Fiegler et al. (2003) 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. As regard to crown rump length, it ranged from 0.60 to 6.90 cm, and there was no significant difference between group A and B (2.72±0.68 vs 2.49±0.76 respectively). On the other hand, gestational sac diameter ranged from 2.20 to 6.50 cm, and there was statistically significant increase in group (A) when compared to group B (3.57±0.49 vs 3.10±0.27 cm respectively). In addition, fetal heart rate ranged from 110 to 182 beat/ minute; and there was statistically significant increase in group (A) (continued) when compared to group (B) (Aborted) (157.37±13.18 vs 121.45±7.08 respectively). These results are comparable to those reported by Maged and Al-Mostafa (2013)who reported that, fetal heart rate (FHR) and Crown Rump Length (CRL) are good ultrasonographic markers for the prediction of outcome in women with threatened abortion. However, and unlike Maged and Al-Mostafa, Al Mohamady et al. (2016)reported that, there was no significant difference between groups as regard to crown rump length, and these results were confirmed in the present work. In addition they reported that, the mean GSD was significantly lower in the group that miscarried compared to the group that continued (P=0.023). The mean FHR was 156.9±20 bpm for the continued group and 122±9 for the aborted group, which showed a statistically significant difference (P<0.001). These results are consistent with the present study.

These results are also in agreement with the study by Falco et al. (2003) who evaluated the outcome and prognostic criteria of pregnancies with first-trimester bleeding and a gestational sac ≤16 mm. They found that of 50 patients, 32 (64%) underwent miscarriage; the size of GSD a high level of statistical significance. However, these results are not in agreement with the study by Oh et al. (2002) who found that the mean diameter of the gestational sac at 28-42 days from the last menstrual period among normal pregnancies did not differ significantly from that in those that subsequently miscarried (2.6 vs. 2.7 mm). This difference can be attributed to the difference in the range of gestational age at which ultrasound was done, 4-6 weeks in their study and 7-13 weeks in our study. Results of the present work (as CRL) also inconsistent with Reljic (2001) who studied 310 singleton pregnancies with live fetuses, presenting with threatened miscarriage before 13 weeks of gestation. He reported that in fetuses with CRL<18 mm, there was a significant positive association between deficit in the CRL for gestation and the incidence of subsequent spontaneous miscarriage. The smaller number of women in our study may explain this difference.Regarding fetal heart rate, results of the present study are in agreement with Doubilet and Benson's (2011) findings. However, when the embryonic heart rate is within the normal range for gestation, the outcome remains uncertain, as in another study done by Tannirandorn et al. (2003). In the present study, there was statistically significant increase of hematoma and pain in patients with abortion in comparison to those who continued their pregnancy. These results are comparable to those reported by Al Mohamady et al. (2016)who reported that, there was a significant difference between women who miscarried and women who continued their pregnancy regarding the presence of sub-chorionic hematoma (SCH) (P=0.002). In addition, these results are in agreement with many studies that showed that SCH was associated with high incidence of 1st trimester miscarriage (Ball et al., 1996).

However, results of the present work are not in agreement with Pearlstone and Baxi's findings (1993). Fourteen studies were reviewed. The incidence of SCH varied greatly among studies from 4 to 48 per cent. They concluded that small SCH tend to be more common in the first trimester and appear to pose no added risk to the ongoing pregnancy but this could be challenged by how small the hematoma needed to be so that to have no adverse effects. In summary, results of the present work revealed that, CA125, fetal heart rate and gestational sac diameter are good predictors for continuity of threatened abortion to complete abortion. In addition, CA125 correlates negatively with heart rate and gestational sac diameters.

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