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DIAGNOSTIC AND PROGNOSTIC ROLE OF SERUM CA-125 IN THREATENED ABORTION : A HOSPITAL BASED COHORT STUDY

Obstetrics & Gynaecology

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ABSTRACT

Introduction: A significant proportion of pregnancies presenting with early bleeding end up in poor outcome (abortion). Present study aim to evaluate CA-125 level as diagnostic and prognostic indicator in threatened abortion. **Material and Methods:** This Hospital based prospective cohort study was conducted included 75 cases of threatened abortion and 75 controls. "Threatened abortion" group included females presenting with 6 to 12 weeks gestation, with a demonstrable fetal heartbeat on ultrasonography, with complain of vaginal bleeding with or without abdominal cramps. 'Threatened abortion' group females were followed and divided into two groups based on their outcome- Threatened abortion ended with Abortion (TAEA) or Threatened abortion with ongoing pregnancy (TAOP). **Results:** Out of the 75 patients with threatened abortion, 27 (36%) ended with abortion. The mean CA-125 levels were found to be significantly higher ($p<0.001$) in TAEA group (89.44 U/ml) as compared to TAOP group (44.69 U/ml) and Control group (24.73 U/ml). A high Area under the ROC curve of 0.916 (95% CI- 0.828 – 1.00) indicated that CA-125 is a good predictor of abortion among females presenting with threatened abortion ($p<0.001$). At the critical cutoff of 58.5 U/ml, CA-125 had sensitivity and specificity of 88.9% and 93.7% respectively for predicting abortion. **Conclusion:** Evaluation of maternal serum CA-125 levels in females with early pregnancy bleeding would allow closer and individualized antenatal monitoring, earlier diagnosis, and timely interventions, which could potentially improve pregnancy outcomes.

KEYWORDS

Abortion, Threatened abortion, CA 125, Early pregnancy loss

Introduction:
Miscarriage is defined as pregnancy loss before 20 weeks or fetus weighing less than 500 grams before it attains a period of viability.[1,2] The term abortion refers to a termination of a pregnancy either naturally/spontaneous or induced till 20 weeks of gestation. Threatened miscarriage is defined as vaginal bleeding before 20 weeks, without cervical dilatation or expulsion of any products of conception, with a live intrauterine gestation on ultrasound finding i.e. with no evidence of fetal demise.[3] In the first trimester terms like miscarriage, spontaneous abortion or early pregnancy loss are used interchangeably

For identifying early pregnancy failure, ultrasonography is probably the best single diagnostic and prognostic test available, however, skill of the operator can have certain constraints and the results may not be consistently reproducible.[4] Maternal serum biochemistry thus has also been proposed as a predictor of the outcome.[5] Many biochemical markers like CA-125, β-HCG, Inhibin, PAPPA-A, S. Progesterone, have been studied to predict its outcome.[21] However, still, challenges prevail regarding the differentiation of normal and abnormal pregnancy.

CA-125 (cancer antigen-125) is a high molecular weight cell-surface antigen.[6] During the first trimester of pregnancy, serum CA-125 levels peak, and drop to non-pregnant values in the second and third trimester. Elevated serum CA-125 levels originate from the decidual cells affected by chorionic invasion or placental separation.[7] High CA-125 can be seen in cancer, Pelvic inflammatory disease, Endometriosis, Uterine fibroids, first trimester of pregnancy, during menstruation, Liver disease, Renal failure, Peritonitis, Pancreatitis, Systemic Lupus Erythematosus and Pericarditis.

Maternal serum CA-125 have been shown to have prognostic value in threatened abortion.[8] Constant or increasing concentrations of CA-125 are observed over 5-7 days among women with threatened abortion who eventually aborted, whereas those who continued with pregnancy had a constantly low or declining CA-125 levels.[9]

As pregnancy loss causes both physical and psychological harm to the female, timely diagnosis and prognosis of threatened abortion is warranted, especially in these times where lower fertility rates are prevailing. Thus present study was conducted with the objective to compare the mean serum CA-125 level among Threatened abortion and Normal pregnancy and its relation to outcome using ROC curve analysis.

Material and Methods:
This Hospital based prospective cohort study was conducted at Department of Obstetrics and Gynaecology, SMS Medical College and Attached Group of Hospitals Jaipur, Rajasthan. The study was conducted from March 2020 to December 2021. A total of 75 cases of threatened abortion and 75 controls were included in the study. "Threatened abortion" group included females presenting between 6 to 12 weeks of gestation, with a demonstrable fetal heartbeat on ultrasonography, with complain of vaginal bleeding with or without abdominal cramps. "Control" group included Next consecutive female presenting presenting between 6 to 12 weeks of gestation, with a demonstrable fetal heartbeat on ultrasonography, without any complaints suggestive of threatened abortion. Pregnant female with ectopic pregnancy, multiple pregnancy, pelvic pathology like history of leiomyoma, endometriosis, past history of infertility, any medical complications, or history of breast, lung, colon, ovarian or endometrial cancers were excluded from the study. The levels of serum CA-125 was assessed by chemiluminescent immunometric method using ADVIA CENTAUR. 'Threatened abortion' group females were followed and divided into two groups based on their outcome- Threatened abortion ended with Abortion (TAEA) or Threatened abortion with ongoing pregnancy (TAOP). All information was recorded using a predesigned semi structured proforma. Ethical clearance was obtained from Institutional Ethics Committee.

Statistical Analysis: Categorical / Nominal variables were summarized as number and percentage and were analyzed using Chi square test. Continuous variables were summarized as mean and standard deviation and were analyzed using One way ANOVA test. Post hoc analysis was done using Tukey test. ROC curve was drawn to evaluate the CA-125 for predicting abortion. Area under the curve was calculated along with its 95% confidence interval and Youden's index was used to determine the critical cutoff value of these parameters. Sensitivity, specificity, positive and negative predictive value and diagnostic accuracy were calculated at the critical cutoff value. A p value ≤ 0.05 was taken as statistically significant. All statistical analysis was done using SPSS version 20 'trial version' statistical software.

Results:
A total of 75 females with threatened abortion and 75 control females (1st trimester normal pregnancy) were included in the study. Out of the 75 patients with threatened abortion, 27 (36%) ended with abortion, while 48 (64%) had ongoing pregnancy at end of 1st trimester. Most of the subjects with both threatened abortion and normal pregnancy were in the age group of 20-29 years. 25.3% controls, 22.9% in TAOP and

18.5% in TAEA groups were Primi gravida. All three groups were comparable with respect to their socio demographic characteristics. More number of previous abortions was significantly associated with TAEA (p=0.018). Pregnant females with gestational age of 6–12 weeks were selected for this study. Most females in Control group (41.3%), TAOP group (39.6%) and TAEA group (55.6%) were in gestational age 10-12 weeks. No significant difference was seen in gestational age among the study groups Table 1).

Lab parameters like TLC, haemoglobin, platelet count, PT, INR were not significantly different (Table 2). The mean CA-125 levels were found to be significantly higher (p<0.001) in TAEA group (89.44 U/ml) as compared to TAOP group (44.69 U/ml) and Control group (24.73 U/ml) (Table 2). Inter group comparison showed significant difference between all the three groups.

A high Area under the curve of 0.916 (95% CI- 0.828 – 1.00) indicates that CA-125 is a good test for predicting abortion among females presenting with threatened abortion (p<0.001). Using Youden's index, the critical cutoff for CA-125 was calculated to be 58.5 U/ml, for this cutoff the sensitivity and specificity for predicting abortion was 88.9% and 93.7% respectively. From a clinician perspective, the PPV was 88.9% and NPV was 93.7%. Overall diagnostic accuracy was 92% (Figure 1).

Table 1: General and Obstetric characteristics of study subjects

	Control (N=75)	TAOP (N=48)	TAEA (N=27)	P value
Age (years)	25.65 ± 3.81	25.04 ± 3.75	27.22 ± 4.72	0.049
BMI (Kg/m^2)	21.43 ± 2.27	21.07 ± 2.52	21.16 ± 2.28	0.682
Gravida				
1	19 (25.3%)	11 (22.9%)	5 (18.5%)	0.360
2	15 (20%)	17 (35.4%)	7 (25.9%)	
3	12 (16%)	11 (22.9%)	6 (22.3%)	
4	19 (25.3%)	4 (8.3%)	5 (18.5%)	
≥5	10 (13.4%)	5 (10.4%)	4 (14.8%)	
Abortion				
0	41 (54.6%)	27 (56.3%)	10 (37%)	0.018
1	21 (28%)	14 (29.2%)	8 (29.6%)	
2	12 (16%)	6 (12.5%)	4 (14.8%)	
3	1 (1.3%)	1 (2.1%)	5 (18.5%)	
Gestational age				
6-7 weeks	20 (26.7%)	13 (27.1%)	4 (14.8%)	0.640
8-9 weeks	24 (32%)	16 (33.3%)	8 (29.6%)	
10-12 weeks	31 (41.3%)	19 (39.6%)	15 (55.6%)	

Table 2: Comparison of lab parameters among study groups

	Control (N=75)	TAOP (N=48)	TAEA (N=27)	P value
TLC (x103/dl)	6.61 ± 1.31	6.37 ± 1.46	6.41 ± 1.72	0.281
Hemoglobin (g/dl)	10.63 ± 1.35	10.56 ± 1.58	10.16 ± 1.68	0.373
Platelet Count (x103/dl)	278.71 ± 89.67	293.48 ± 80.03	287.48 ± 96.78	0.655
Prothrombin Time (sec)	11.75 ± 1.75	11.38 ± 1.75	11.07 ± 1.17	0.161
INR	1.05 ± 0.03	1.05 ± 0.03	1.05 ± 0.03	0.988
CA-125 Levels (U/ml)	24.73 ± 13.76	44.69 ± 16.91	89.44 ± 23.2	<0.001

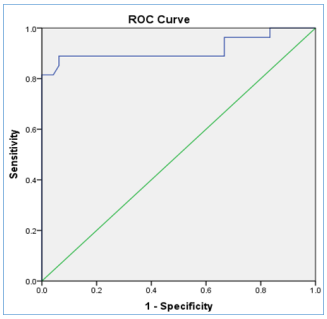

Figure 1: ROC Curve for CA-125 for Predicting Abortion among females presenting with threatened abortion

Discussion:

Early threatened abortion can either lead to continuation or termination of pregnancy. Thereby, early diagnosis and prognosis assessment is important for these pregnancies. This study evaluates serum CA-125 in early threatened abortion. Most of the subjects with both threatened abortion and normal pregnancy were aged 20-29 years. Mean age of control, TAOP and TAEA subjects was 25.65±3.81, 25.04±3.75, 27.22±4.72 years respectively (p>0.05). Past studies from India have reported mean age of females presenting with threatened abortion around 25 years. [10-12]

Primigravida were seen in 25.3% controls, 22.9% in TAOP and 18.5% in TAEA groups, with no significant difference between the groups. In a similar study, Sudha et al (2020) found that maximum numbers of patients were primigravida (55%).[12] This variation could be due to different study site and selection criteria. In present study, gestational age was not found to be associated with outcome, as has been similarly reported by past studies. [11,12]

The mean CA-125 levels were found to be significantly higher in TAEA group (89.44±23.2 U/ml) as compared to TAOP group (44.69±16.91 U/ml) and in Control group (24.73±13.76 U/ml). In a similar study Sedigheh Ayaty (2007) observed that the mean CA-125 in finally aborted patients was 58.17±7.25 IU/ml and in those who continued and did not abort, was 30.89 IU/ml, while in normal pregnant women, who continue to term, was 26.61±1.76 IU/ml.[13]

B Mahdi (2009) also found that higher mean value of CA-125 observed for the group that ended with abortion. [14] Dr. Aruna Bhattacharya et al (2015) observed that the mean CA-125 values were 131±4.80 versus 35.95±22.1 U/mL for miscarriages and successful pregnancies, respectively, while in normal pregnancies the respective value was 32.5±4.2 U/mL.[10]

Helema and Ishra (2016) revealed that CA-125 was significantly higher in threatened miscarriage ended by abortion group (73.48 ± 20.29 lU/ml), as compared to threatened miscarriage ongoing (13.69 ± 4.01 U/ml) and control group (11.73 ± 4.74 IU/ml) respectively. [15]Abd-Elrauof M Oun et al (2018) found that CA-125 levels was significantly decreased in continued group when compared to aborted group (19.45±5.57 v/s 53.83±9.48 respectively). [16] Dr. Chitra Gidwani et al (2019) found that among patients of threatened abortion who aborted, mean maternal serum CA-125 level was (148.011 IU/ml) significantly raised compared to patients of threatened abortion who progressed normally to the period of viability (34.75IU/ml).[11] In yet another similar study done recently, Dr. Sudha et al (2020) found that among patients of threatened abortion who aborted, mean maternal serum CA-125 level was (117.06 IU/ml) significantly raised as compared to patients of threatened abortion who progressed normally to the period of viability (49.11 IU/ml). [12]

Many other past studies have shown significantly higher CA- 125 among threatened abortion ending in abortion group than complete pregnancy group and controls.[17-20]

A high Area under the ROC curve of 0.916 (95% CI- 0.828 – 1.00) indicated that CA-125 is a good predictor of abortion among females presenting with threatened abortion. At the critical cutoff of 58.5 U/ml, the sensitivity and specificity for predicting abortion was 88.9% and 93.7% respectively. In a similar study, Rekha N. Pillai et al (2016) reported that CA125 had a sensitivity of 90% and specificity of 88% for predicting abortion.[4] Dr. Ela Jha et al (2019) found that Serum CA-125, was an independent predictor, with statistically significant sensitivities in predicting pregnancy outcome in cases of threatened abortion.[21] Abd-Elhaseib Salah et al (2019) observed that CA-125 was good predictor of pregnancy loss.[19] Yehia A. Wafa et al (2017) found that a patient with a lower level of CA-125 than 51.68U/ml is an excellent predictor of pregnancy outcome in women with threatened abortion.[22]

Conclusion:

A significant proportion of pregnancies presenting with early bleeding, finally end up in poor outcome (abortion). The estimation of maternal serum CA-125 can accurately predict outcome in females with early pregnancy bleeding. Thus, evaluation of maternal serum CA-125 levels in females with early pregnancy bleeding would allow closer and individualized antenatal monitoring, earlier diagnosis, and timely interventions, which could potentially improve pregnancy outcomes.

Multicentric prospective studies are required to accurately establish the optimal cut off levels of serum CA 125 for different gestational age and to establish them as prognostic tool

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