Cancer antigen 125 (CA-125) and serum progesterone as predictors of fate of threatened abortion: Case control study

Case Control Study

Marwa Eid[1] and Amal Kotb Abdallah[2]

[1]*Obstetrics and Gynecology Department, Faculty of Medicine, Cairo University*

[2]*Obstetrics and Gynecology Department, Faculty of Medicine, Beni-Suef University, Egypt*

ABSTRACT

Objective: To investigate the predictive value of serum progesterone and CA-125 regarding pregnancy continuation in women with threatened abortion.

Patients and Methods: A case control study was conducted on 200 women with intrauterine pregnancies between 6-12 weeks with demonstrable embryonic pulsation. They were classified into 2 groups: Group I included 100 women with the diagnosis of threatened abortion. Group II included 100 women with normal asymptomatic pregnancy.CA 125 and serum progesterone were measured in all women.

Results: Women with threatened abortion showed a significantly higher number of previous abortions and CA 125 levels (47.82±30.93 vs. 30.08±19.21, P =0.36) and lower rate of pregnancy continuation (76 vs. 90%, P = 0.044) when compared to controls. Women who continued their first trimester of pregnancy showed a significantly higher number of previous abortions and progesterone level (43.12±20.85 vs. 19.26±11.8, P = 0.01) and lower level of CA 125 (34.9±11.053 vs. 61.9±19.21, P = 0.022) when compared with those who aborted. The sensitivity, specificity, PPV and NPV of CA 125 and progesterone in predicting occuarance of abortion were (80.66, 100,100,95.4% and 78.88,97.05,93.7,01.3% respectively.

Conclusion: CA125 and progesterone are good predictors for the outcome of 1st trimester of pregnancy in both normal women and those with threatened abortion. Both have excellent specificity and good sensitivity in prediction of the outcome.

Key Words: CA 125, predictors of pregnancy outcome, serum progesterone, threatened abortion

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Corresponding Author: Amal Kotb Abdallah, Obstetrics and Gynecology Department, Beni-Suef University, Beni-Suef, Egypt, **Tel.:** 01065059597, **E-mail:** amalkotb7295@yahoo.com

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INTRODUCTION

The National Center for Health Statistics, the Centers for Disease Control and Prevention, and the World Health Organization all define abortion as pregnancy termination before 20 weeks' gestation or with a fetus born weighing < 500 g [1]. More than 80 percent of spontaneous abortions occur within the first 12 weeks of gestation. The clinical diagnosis of threatened abortion is presumed when bloody vaginal discharge or bleeding appears through a closed cervical os during the first 20 weeks [2]. Almost a fourth of women develop clinically significant bleeding during early gestation that may persist for days or weeks. Bleeding is by far the most predictive risk factor for pregnancy loss [3]. Overall, approximately half will abort, but this risk is substantially less if there is fetal cardiac activity [4]

About 12% of pregnancies in which bleeding occurred ended in miscarriage. Other studies reported higher rates (16%) [5]. The etiology is often unclear and may be multifactorial, causes include genetics, anatomical, endocrine, hormonal problems. Other underlying factors include certain infectious factors; smoking, alcohol consumption, exposure to environmental risk factors, psychological trauma and stressful life events as well as certain coagulation and immunoregulatory protein defects [6].

Progesterone also known as P4 (pregn-4-ene-3, 20-dione) is a C-21 steroid hormone involved in regulation of the female menstrual cycle. It also plays an important role during pregnancy to support gestation [7]. Progesterone acts to block the oxytocin effect of prostaglandin F2a and an adrenergic response [8]. It also suppresses calcium-calmodulin-myosin light chain kinase system. Reducing calcium influx ad alternating resting potential of smooth muscle [9].

CA-125 is a cell-surface antigen expressed by

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derivatives of the coelomic epithelium that is well established as a useful marker for the monitoring of women with epithelial ovarian cancer. Levels of CA-125 are often elevated in women with advanced endometriosis [10] in early pregnancy, during normal menstruation, and in women with acute pelvic inflammatory disease or leiomyomas [11]

Some studies detected that the abortion risk is increased in pregnant women with higher CA125 levels [12]. Others could not find a statistically significant difference in the CA125 levels when abortion cases were compared with the cases of continuing pregnancy [13]

CA-125 level in threatened abortion is an inexpensive, easily available, sensitive and specific predictor of outcome in threatened abortion, which results the loss of pregnancy [14].

The aim of this work is to investigate the predictive value of serum progesterone and CA-125 regarding pregnancy continuation in women with threatened abortion.

PATIENTS AND METHODS:

This case control study was conducted on 200 pregnant women attended the obstetric clinic at kasr Alainy medical school at Cairo university from May 2014 to December 2016. All participants had intrauterine pregnancies between 612- weeks with demonstrable embryonic pulsation. They were classified into 2 groups: Group I included 100 women with the diagnosis of threatened abortion with mild vaginal bleeding and closed inner os. Group II included 100 women with normal asymptomatic pregnancy. All women ages ranged from 20 to 40 years old.

Exclusion criteria included women with blighted ovum or multiple gestation, ectopic pregnancy and cases concieved through assisted reproductive techniques.

All women were subjected to proper history taking with detailed obstetric history and full clinical examination. Gestational age was determined according to the sure dates of the last menstrual period and confirmed with ultrasound evaluation. Transvaginal ultrasound examination was done using transvaginal 5 MHZ transvaginal probe to assess embryonic or fetal pulsations and confirmation of gestational age using (Voluson 58-GE ultrasound Korea. ltd.9. Sunhwan-ro-214beon-gil,Gyneonggi-do,Korea).

Blood was obtained from an antecubital vein and the serum was separated and frozen at -70°C until assayed. CA-125 is measured by the Electrochemiluminescence Immunoassay (ECLIA) using the Immulite 2000 instrument using kits supplied by DPC (DPC, Los Angeles, USA). intended for used on Elecsys and Cobase the immunoassay analyzers.

The principle of measuring progesterone level by the Electrochemiluminescence Immunoassay (ECLIA) using kits supplied by Roche (Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim) is intended for use on Elecsys and Cobase immunoassay analyzers.

The data collected were tabulated & analyzed by SPSS (statistical package for the social science software) statistical package version 11 on IBM compatible computer. Quantitative data were expressed as mean & standard deviation (X+SD) and analyzed by applying student t-test for comparison of two groups. Qualitative data were expressed as number and percentage (No & %) and analyzed by applying chi-square test. Roc curve (Receiver operating characteristic curve): was done to detect cut level of any tested variable. The validity of the model was measured by means of the concordance statistic (equivalent to the area under the Roc curve). A model with a c value above 0.7 is considered useful while a c value between 0.8 and 0.9 indicated excellent diagnostic accuracy.

RESULTS

There was no significant diffrence between women with threatened abortion and those with normal pregnancy regarding maternal age, gestational age , parity and serum progesterone level (table 1).

Women with threatened abortion showed a significantly higher number of previous abortions and CA 125 levels and lower rate of pregnancy continuation when compared to controls (table 1).

Table (1): Characteristics and hormonal assessment among women with threatened abortion and controls

		Threatened	Normal	P value
Age (years)		25.35±5.06	23.2±3.5	0.122 NS
GA (weeks) #		8.8±1.36	8.2±1.06	0.128 NS
Parity *	P0	47	55	0.145 NS
	P1	21	34	
	P2	22	6	
	P3	6	2	
	P4	4	3	
No previous abortions*	0	74	95	0.017 S
	1	26	5	
Pregnancy continuation*	Yes	76	90	0.044 S
	Aborted	24	10	
Hormonal levels	CA.125(IU/ml)	47.82±30.93	30.08±19.21	0.036 S
	Progesterone(ng/ml)	38.11±40.85	40.98±61.18	0.862 NS

Data are presented as mean ± SD
* Data are presented as number (percentages)
# GA gestational age

There was no significant diffrence between women who continued the first trimester of pregnancy and those who aborted regarding maternal age, gestational age and parity (table 2).

Women who continued their first trimester of pregnancy showed a significantly higher number of previous abortions and progesterone level and lower level of CA 125 when compared with those who aborted (table 2).

Table 2 *:* Characteristics and hormonal assessment among women with continued pregnancy and with abortion

		Continued	Aborted	P value
Age (years)		23.7±4.2	27.5±4.96	0.052NS
GA (weeks)		8.8±1.36	8.2±1.06	0.128 NS
Parity*	P0	86 (51.8%)	16 (47.1%)	0.282 NS
	P1	45 (27.1%)	10 (29.4%)	
	P2	24 (14.4%)	4 (11.8%)	
	P3	5 (3.0%)	3 (8.8%)	
	P4	6 (3.6%)	1 (2.9%)	
No previous abortions*	0	144 (86.7%)	25 (73.5%)	0.017 S
	1	22 (13.3%)	9 (26.5%)	
Hormonal levels	CA.125(IU/ml)	34.9±11.053	61.9±19.21	0.022 S
	Progesterone(ng/ml)	43.12±20.85	19.26±11.8	0.010 S

Data are presented as mean ± SD
* Data are presented as number (percentages)
# GA gestational age

The sensitivity, specificity, PPV and NPV of CA 125 and progesterone in predicting occuarance of abortion are shown in table 3 and figure 1.

Table 3 : ROC curve analysis for prediction of the occurrence of miscarriage

	AUC	Sensitivity	Specificity	PPV	NPV
CA.125 (IU/ml)	0.965	80.66	100	100	95.4
Progesterone (ng/ml)	0.877	78.88	97.05	93.7	91.3

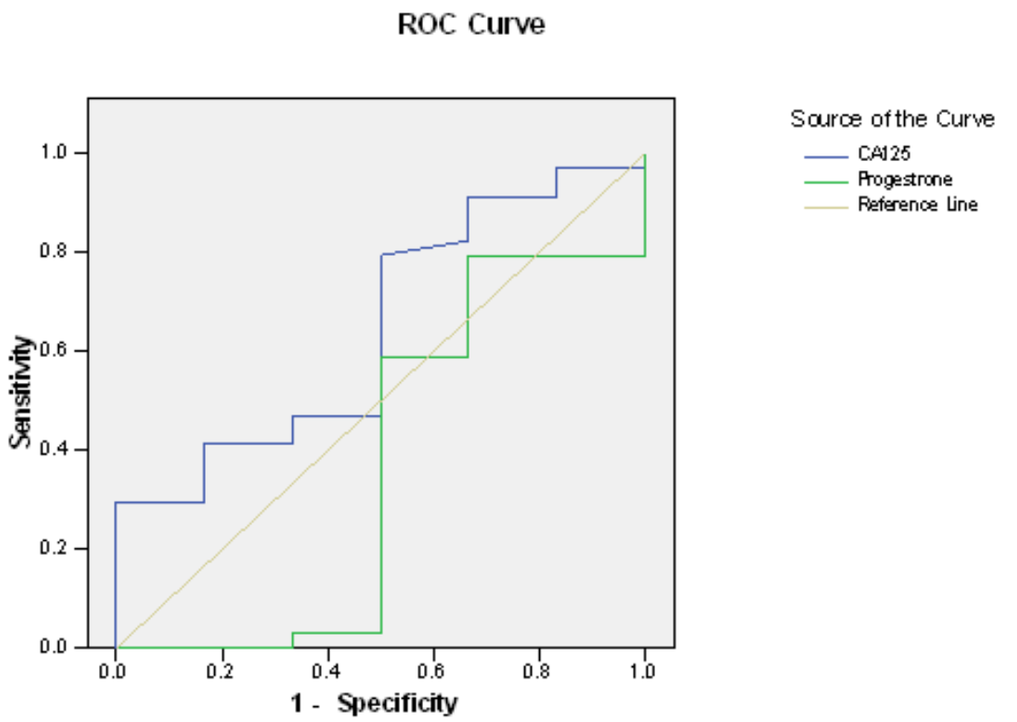

Fig. 1 : ROC curve for prediction of the occurrence of miscarriage using CA125 and progesterone levels.

DISCUSSION

CA-125 and progesterone are good predictors for the outcome of 1st trimester of pregnancy in both normal women and those with threatened abortion. Both have excellent specificity and good sensitivity in prediction of the outcome.

In our study, there was a a higher level of serum progesterone and lower level of CA-125 in women who passed through their first trimester safely. Progesterone induce secretory changes in the lining of the uterus essential for successful implantation of a fertilised egg. It is secreted chiefly by the corpus luteum. It has been suggested that a causative factor in many cases of miscarriage may be inadequate secretion of progesterone during the luteal phase of the menstrual cycle and in the early weeks of pregnancy. Therefore, progestogens have been used, beginning in the first trimester of pregnancy, in an attempt to prevent spontaneous miscarriage. Their use is particularly common with assisted reproductive technologies [7].

Progesterone has a role in maintaining pregnancy by suppression of calcium-calmodulin-myosin light chain kinase system. Reducing calcium influx and alternating resting potential of smooth muscle. It is actively metabolized by the uterus to a number of 5α

and 5β metabolites intringuinly, many of metabolites of progesterone are more potent than progesterone in inhibiting uterine contractility [15].

Viable intrauterine pregnancy is associated with good levels of serum progesterone above 55 nmol/L [16]. This may be a normal sequelae of adequate corpus luteal function and adequately formed placenta [17] and failure of pregnancy is usually associated with lower serum progesterone less than 30 nmol/L) [18].

CA-125 antigen in sera of pregnant women is derived from the decidual cells following their invasion by trophoblastic cells [19]. CA-125 is produced by the endometrium and is suggested to be a marker of endometrial receptivity so it is related to endometrial function with an endocrine or a paracrine function so its relation to pregnancy failure can be explained [20].

Maged and Mostafa in 2013 performed their observational study on 250 women during the first 12 weeks of gestational age to evaluate the predictivity of biochemical and ultrsonographic markers in women with threatened abortion. They classified the participants into 3 groups. Group 1 included 65 women with failure of pregnancy continuation after threatened abortion, group 2 included 85 women with continuation of pregnancy after having threatened abortion and group 3 included 100 women with normal pregnancy. They found significant difference regarding the levels of CA-125 and progesterone between group 1 and other 2 groups. They concluded that measurements of these markers are good predictors for pregnancy outcome in cases of threatened abortion [12].

Bon *et al*. (2001) stated that CA125 serum level increases during first trimester of pregnancy than that in non-pregnant women. This elevation is exaggerated in cases with threatened symptom to the extent that the patients who are presented the highest level of the antigen did abort later [21].

Many studies 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 [14].

Abdel Azim *et al*. (2012) detected the relation between serum progesterone and viability of the pregnancy during the first trimester. The mean serum progesterone of the studied population was significantly high in viable pregnancy group compared to non-viable pregnancy group. They concluded that serum progesterone is a reliable marker for early pregnancy failure and single assay of its serum level can differentiate between viable and non-viable pregnancies [22].

Several cutoff values for serum CA-125 level were suggested to discriminate between viable and non-viable gestations at time of vaginal bleeding. Azougi *et al*. (1996) used a 125 IU/ml as a cutoff value and reported a 100% sensitivity and specificity [23]. Schmidt *et al*. (2001) used a 65 IU/ml as a cutoff value and reported sensitivity 50% for this level [24]. Fiegler *et al*. (2003) used a cutoff value of 66.5 IU/ml with sensitivity of 55% [25].

The main limitation of our study was absence of long term follow up to ensure non occurance of 2nd trimesteric abortion and preterm birth as after the end of the first trimester there was a very high drop out cases so statistical evaluation would be of no value.

The ideal assay would predict pregnancy outcome from a single serum sample in patients with symptoms of threatening miscarriage. As the main purpose of introducing estimation of biochemical parameters in patients of early pregnancy bleeding is to identify failing gestation and thus correlate treatment.

This study suggested the possibility of using a single serum CA-125 and progesterone for the prediction of risk of pregnancy loss in cases of first trimesteric threatened abortion are sensitive and accurate predictors of pregnancy outcome.

It is recommended that at least a repeated fetal ultrasound during the first trimester is done if fetal viability is established sonographically at 78- weeks of gestation with high CA-125 level or low level of progesterone in cases of threatened miscarriage.

Also, it is recommended that patients who have CA-125 more than 58 IU/ml should be prepared for poor prognosis of their current pregnancy spare them the expenses and complications of anxiety that may ensue prior to definitive therapy and on the other hand patients who have serum CA-125 less than 58 IU/ml should be reassured regarding the favorable prognosis of their pregnancy outcome and encouraged to follow the instruction of their obstetrician and to rest mentally and physically.

It also recommended that patients who have progestrone levels >22 ng/ml have a high probability of viable intrauterine pregnancy.

CONFLICT OF INTEREST

There is no conflict of intersest.

REFERENCES

1. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ and Sponge CY. Abortion . In: Cunningham FG, Williams JW, editors. William's obstetrics. 24th ed. New York (NY): McGraw-Hill; 2014. Chapter 18 p.350- 376

2. Hasan R, Baird DD, Herring AH, *et al:* Association between first-trimester vaginal bleeding and miscarriage. Obstet Gynecol 2009; 114:860

3. Eddleman K, Sullivan L, Stone J, *et al*: An individualized risk for spontaneous pregnancy loss: a risk function model. J Soc Gynecol Investig 2006; 13:197A

4. Tongsong T, Srisomboon J, Wanapirak C, Sirichotiyakul S, Pongsatha S, Polsrisuthikul T.: Pregnancy outcome of threatened abortion with demonstrable fetal cardiac activity: a cohort study. J Obstet Gynaecol 1995; 21:331.

5. Everett C. Incidence and outcome of bleeding before the 20th week of pregnancy: prospective study from general practice. BMJ 1997;315:32–4.

6. Li TC, Makris M, Tomsu M, Tuckerman E, Laird S. Recurrent miscarriage etiology, management and prognosis. Hum Reprod Update 2012; 8: 463- 81.

7. Goodson WH III, Handagama P, Moore DH II, Dairke S. Milk products are a source of dietary progesterone. 30th Annual San Antonio Breast Cancer Symposium 2007; pp. abstract 2028. Retrieved 200812-3 0-

8. Thornton JG . Maintenance tocolysis. BJOG 2005; 112(Suppl 1): 118 -121.

9. Tita AT and Rouse DJ. Progesterone for preterm birth prevention: An evolving intervention. Am J Obstet Gynecol 2009; 200: 219 -224.

10. Osmanagaoglu MA, Erdogan I, Eminagaoglu S, Karahan SC, Ozgun S, An GC, Bozkaya H. The diagnostic value of b-human chorionic gonadotropin, progesterone, CA125 in the prediction of abortions. J Obstet Gynaecol 2010;30(3):288–93.

11. Koninckx PR, Riittinen L, Seppala M, Cornillie FJ. CA-125 and placental protein 14 concentrations in plasma and peritoneal fluid of women with deeply infiltrating pelvic endometriosis. Fertil Steril 1992;57:523.

12. Maged AM and Mostafa WA. Biochemical and ultrasonographic predictors of outcomein threatened abortion. Middle East Fertility Society Journal 2013; 18, 177–181

13. Check JH, Nowroozi K, Winkel CA, Johnson T, Seefried L. Serum CA-125 levels in early pregnancy and subsequent spontaneous abortion. Obstet Gynecol 1990;75:742–4.

14. Ayaty S, Roudsari FV and Tavassoly F . CA-125 in normal pregnancy and threatened abortion. Iranian Journal of Reproductive Medicine 2007; 5(2): 57- 60.

15. Arkaraviehien W and Kendle KE. Critical progesterone requirement for maintenance of pregnancy in ovariectomized rats. J Reprod Fertil 2010; 90: 63- 70.

16. Hornstein MD, Check JH, Hill JA. Serum CA 125 levels and spontaneous abortion Februmy. Am J Obstet Gynecol 1995:695–9.

17. Sherif LS, El-Metwaly AG, Shalan H, Badawy AM, Abu-Hashem E. Can a single serum CA125 assay predict the outcome of threatened abortion? J Obstet Gynaecol 2000;20(1):65–7.

18. Bignardi T, Condous G, Kirk E, Van Calster B, Van Huffel S, Timmerman D, Bourne T. Viability of intrauterine pregnancy in women with pregnancy of unknown location prediction using human chorionic gonadotropin ratio vs. progesterone. Ultrasound Obstet Gynecol. 2010 Jun;35(6):65661-. doi: 10.1002/uog.7669.

19. Argiieso P, Guzman-Aranguez A, Mantelli F, Cao Z, RicciutoJ and Panjwani N. Association of cell surface mucins with galectin-3 contributes to the ocular surface epithelial barrier. J Biol Chem 2009; 284: 23037- 23045.

20. Brandenberger AW, Bersinger NA, Huber PR, Berger E, Glanzmann P, Birkhaeuser MH. CA-125 concentrations in the serum and pregnancy outcome in IVF cycles. J Assist Reprod Genet. 1998 Jul; 15(6):390- 4.

21. Bon GG, Kenemans P, Verstraeten AA, Go S and Philipi PA. Maternal serum Cal25 and Cal53- antigen levels in normal and pathological pregnancy. Fetal DiagnTher 2001; 16: 166- 172.

22. Abdel Azim IA, Abo Elezz A and El-sherbiny M . Relation between single serum progesterone assay and viability of the first trimester pregnancy. Springerplus 2012; 1(1): 80.

23. Azogui G, Yaronovski A, Zohar S and Ben-Shlomo I. CA-125 is elevated in viable pregnancies destined to be miscarried: a prospective longitudinal study. Fertil Steril 1996; 65: 1059- 1061.

24. Schmidt T, Rein DT, Foth D, Eibach HW and Kurbacher CM. Prognostic value of repeated serum CA 125 measurements in first trimester pregnancy. Eur J Obstet Gynecol Reprod Biol 2001;97: 168- 173.

25. Fiegler P, Kaminski K, Wegrzyn P. Serum levels of CA-125 antigen during the first trimester of pregnancy complications and the risk of miscarriage. Ginekol Pol 2003; 74: 345 -349.