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ORIGINAL ARTICLE

Diagnostic value of progesterone and CA-125 in the prediction of ectopic and abortive intrauterine gestations

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Objective: The study was designed to investigate the predictive value of progesterone and CA-125 in the diagnosis of ectopic pregnancy (EP) and inevitable miscarriage.
Methods: Forty women with EP, 20 with intrauterine (IU) abortive gestation and 20 regular pregnant women (controls) were studied. IU abortive and EP were confirmed and treated by surgery. Serum progesterone and CA-125 levels were measured at the time of presentation and 24 hours after surgery.
Results: Women with EP had significantly lower progesterone concentrations, compared to both women with IU abortive pregnancy and controls. Women with IU abortion had significantly higher CA-125 levels, compared to the other two groups. When using a progesterone concentration of less than 10.75 ng/ml as a cut-point for the diagnosis of EP, sensitivity, specificity, positive and negative predictive values were 85%. When using CA-125 concentration of more than 41.9 U/ml as a threshold for the diagnosis of IU abortive pregnancy, sensitivity was 80%, specificity 87%, the positive predictive value was 66% and the negative predictive value 93%.
Conclusion: The measurement of progesterone and CA-125 levels is useful in discriminating ectopic and intrauterine abortive from normal gestations. *Hippokratia 2005; 9 (3): 124-129*

Key words: *ectopic pregnancy, abortive gestation, progesterone, CA-125*

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Ectopic pregnancy (EP) is a relatively common complication, which can be fatal, if it is not promptly diagnosed[1]. Inevitable miscarriage (intrauterine abortion) is another common gynecological cause of abdominal pain, which must be distinguished from EP[1]. Several methods have been proposed to support clinical and sonographic evidence and aid the differential diagnosis between these two conditions[1-3].

Decreased chorionic gonadotropin (hCG) production by the abnormally growing fetal tissue has been used as a predictor of EP[2], with serial measurements being of more significant diagnostic value[3]. However, it soon became evident that relatively low hCG levels and the lack of a normal fetoplacental unit also result in reduced progesterone production by the corpus luteum[4]. Therefore, a single measurement of progesterone levels has been reported to help in the diagnosis of abnormal pregnancy in general[5-10], or EP in specific[11-19].

Nevertheless, in numerous studies it has also been suggested that circulating progesterone cannot differentiate between EP and spontaneous abortion[5-7], or even that it is not a reliable marker at all[20-22]. This was basically due to a significant overlap between values. It should be noted that, according to a recent meta-analysis of the above studies[23], reduced progesterone levels can identify patients at risk for EP, but the discriminative capacity of a single progesterone measurement is relatively poor.

The CA-125 tumor marker is a cell-surface antigen derived from the surface coelomic epithelium, including the mucosa of the entire female genital tract and maternal decidua[24,25]. Therefore, extensive tissue destruction in both tubal[26] and uterine[27] abortions has been shown to result in a significant increase of CA-125 levels. It has also been suggested that high CA-125 levels are predictive of spontaneous abortion in the first trimester of pregnancy[28], although in another study[29] no significant predictive value was found.

In women with ectopic pregnancies, the extrauterine compartments are exposed to fetal tissue, which is also known to express substantial amounts of CA-125[24]. One study has demonstrated increased concentrations of this marker in women with EP, compared to those of women with normal intrauterine gestation[30]. However, in another report, women with ectopic pregnancy had lower CA-125 levels, compared to regular pregnant women[31].

Given the above conflictive evidence and the need for reliable predictors in the diagnosis of EP and uterine abortion, the present study was designed in order to further investigate the diagnostic value of serum progesterone and CA-125 levels in everyday clinical practise. Notably, no previous studies of CA-125 levels involving all three sub-groups (women with EP, IU abortion and normal pregnancy) were found in the literature.

Materials and Methods

Subjects

Forty women with ectopic pregnancy (EP), 20 with intrauterine (IU) abortion (inevitable miscarriage), and 20 regular women with normal IU gestation (controls) were studied. Serum samples from all 80 women were collected. Diagnosis of IU or ectopic pregnancy was based on clinical assessment and transvaginal ultrasonography (U/S). Intrauterine abortive and ectopic pregnancies were confirmed and treated by surgery.

From all women, blood was drawn by routine venipuncture at the time of presentation and 24 hours after surgery in the sub-groups of women with EP and intrauterine abortion. Blood samples were centrifigured at 3,000 rpm and serum was stored at -60°C. Informed consent was obtained from all women, and the study was approved by the local institutional review board and ethical committee.

Assays

Human Chorionic Gonadotropin (hCG), progesterone and CA-125 levels were measured with commercial Microparticle Enzyme Immunoassay (MEIA) kits (Abbott Laboratories, Diagnostics Division, Abbott Park IL, 60064, USA). The intra-assay coefficients of variation (CV) ranged from 1.11 to 2.55% for hCG, from 1.14 to 5.87% for progesterone, and from 3.0 to 4.5% for CA-125. The inter-assay coefficients of variation ranged from 3.54 to 3.98% for hCG, from 6.67 to 9.58% for progesterone, and from 2.8 to 3.04.5% for CA-125.

Data analyses

Values are presented as mean±standard deviation (SD) in tables and as mean+standard error for mean (SEM) in graphs. The Kolmogorov-Smirnov (K-S) test was used to test the normality of distribution. Comparison of means between different groups was performed with Student's t-test for normal and Mann-Whitney U-test for non-normal values. Comparison of values at the time of presentation and 24 hrs after treatment were performed with the paired t-test for normal and the Wilcoxon test for non-normal values. Adjustment of means was performed by means of general linear model (GLM)-based univariate analysis of covariance (ANCOVA).

Receiver Operator Characteristic (ROC) curves[32] were constructed to plot sensitivity against specificity of low progesterone and high CA-125 levels as diagnostic tests for EP and IU abortive pregnancy, respectively. The areas under the ROC curves (AUC) were calculated and compared with the AUC (0.5) of the non-diagnostic test (the line with slope of 1). For cut-off values of significant sensitivity and specificity (>80%), contingency tables (cross-tabs) were constructed for the calculation of positive and negative predictive values. Confidence intervals of sensitivity, specificity, positive and negative predicted values were calculated with Wilson's method by CIA software (v. 2.0.0, Southampton, UK). All other analyses were performed by SPSS software (v.11.5 SPSS, Inc., Chicago, IL, USA). The level of statistical significance was set at 5%.

Results

The basic anthropometric, clinical and hormonal parameters of the women studied are summarized in Table 1. A significant difference in age ($P<0.01$) and BMI ($P<0.001$) was observed between women with EP and those with normal intrauterine gestation, and in gestational age ($p=0.001$) and BMI ($p<0.05$) between women with EP and women with intrauterine abortive pregnancy. Adjustments for the above parameters were performed where appropriate.

Human chorionic gonadotrophin levels were significantly lower in EP and abortive IU gestations, compared to normal pregnancies and in women with ectopic gestation, compared to those with inevitable miscarriage ($p<0.001$). All differences remained statistically significant after adjustment for the duration of pregnancy. hCG levels were significantly decreased after surgical treatment only in the sub-group of women with EP ($p<0.01$).

Progesterone levels were significantly lower in women with EP, compared to those of women with IU abortion ($p<0.01$) or normal pregnancy ($p<0.001$). Controls had significantly higher progesterone levels, compared to women with abortive gestation ($p<0.01$). All differences were blunted

Table 1. *Basic anthropometric, clinical and hormonal parameters of the women studied at the time of presentation and 24 hours after surgical treatment [mean±SD (minimum-maximum), statistical significance]*

	Type of Pregnancy		
	Ectopic (n=40)	Intrauterine abortive (n=20)	Intrauterine normal (n=20)
Age (years)	28.1±6.3 † (16.0-37.0)	(18.0-39.0) 24.6±2.7	26.9±4.9 (21.0-32.0)
BMI (kg/m²)	23.9±2.5 †* (18.8-31.6)	18.5-31.3 21.3±2.1	22.4±2.6 (16.5-25.5)
Weeks of Pregnancy	5.8±0.9 * (4.0-10.3)	(3.0-9.3) 6.3±1.0	6.8±1.0 (3.0-8.0)
hCG (mU/ml)	8680.9±8821.6*† (472.0-103599.0)	(100.0-45741.0) 66930.9±32522.2	24724.0±21105.0† (2387.0-137962.0)
hCG 24 hrs after	2823.4±2246.5*‡ (350.0-94933.0)	(69.0-10459.0) –	27536.9±20250.0 –
Progesterone (ng/ml)	7.9±3.4 †* (1.0-22.7)	(0.6-18.5) 15.9±3.4	11.5±4.9 † (4.5-23.9)
Progesterone 24 hrs after	3.9±2.9 *‡ (1.06-17.0)	(1.0-15.1) –	6.7±3.3 ‡ –
CA-125 (U/ml)	32.4±20.1 * (10.5-277.1)	(5.7-109.6) 29.8±10.7	59.5±54.3 † (8.4-53.9)
CA-125 24 hrs after	35.3±17.9 ‡ (10.2-109.1)	(4.5-102.3) –	45.6±22.7 ‡ –

† $P<0.05$ ectopic or intrauterine abortive vs normal
* $P<0.05$ ectopic vs intrauterine abortive
‡ $P<0.05$ vs value at the time of presentation

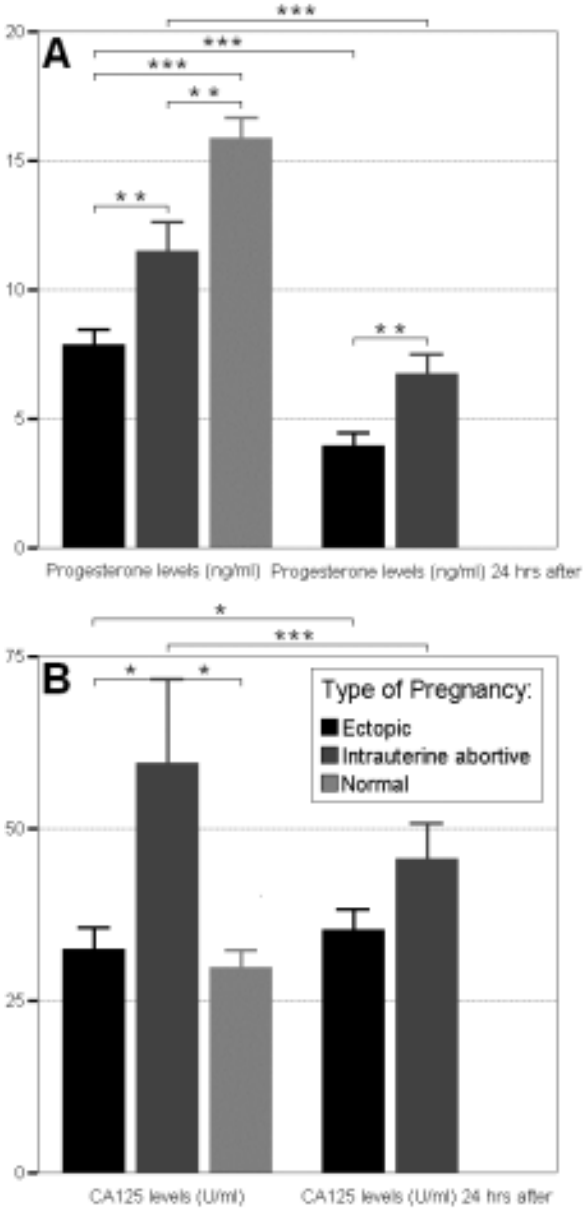

Figure 1. *Circulating levels of progesterone (A) and CA-125 (B) at the time of diagnosis and 24 hours after surgical treatment. Values are presented as mean + SEM*
** p<0.05, ** p<0.01, *** p<0.001*

after adjustment for weeks of pregnancy, but remained statistically significant (p<0.05). After surgery, progesterone levels were decreased in both women with EP and those with IU miscarriage (p<0.001), and the difference between the two remained significant (p<0.001) (Figure 1A).

CA-125 levels were significantly higher in the group of women with intrauterine abortive pregnancy, compared to both women with EP and controls (p<0.05). In this particular group, CA-125 levels fell significantly after treatment (p<0.001), while in women with EP a slight increase was observed (p<0.05). As a consequence, after 24 hrs, the difference between the two was no longer significant (Figure 1B).

The ROC curves demonstrated a significant discriminatory ability of decreased progesterone and increased CA-125 levels for the diagnosis of ectopic and abortive uterine gestations, respectively. The AUC for progesterone was 0.859 (95% CI: 0.768-0.951) and the AUC for CA-125 was 0.788 (95% CI: 0.639-0.957). When plotted against the AUC for the non-diagnostic test (0.5), a significant difference was found in both comparisons (p<0.001) (Figures 2 and 3).

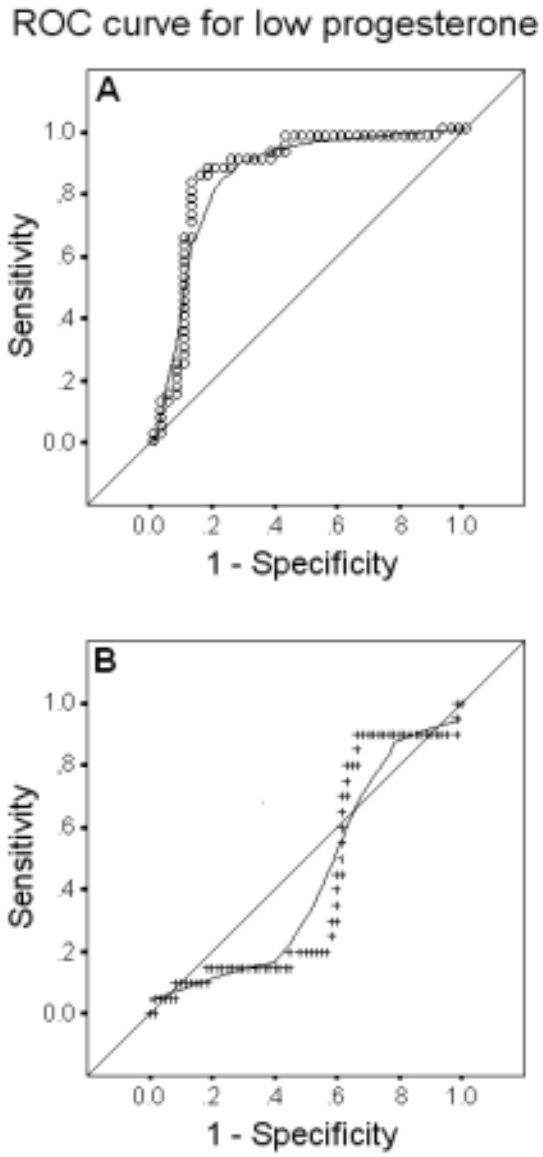

Figure 2. *Receiver Operator Characteristic (ROC) curves of low progesterone levels as diagnostic tests for ectopic (A:?) or intrauterine (B:+) abortive gestation. The smallest cut-off value is the minimum observed test value minus 1 and the largest cut-off value is the maximum observed test value plus 1. All the other cut-off values are the averages of two consecutive ordered observed test values. The diagonal line with slope of one (AUC = 0.5) represents the theoretical test of no discriminatory value. $AUC_{ectopic}$ = 0.859 (95% CI: 0.768-0.951, P<0.001), $AUC_{abortive}$ = 0.433 (95% CI: 0.295-0.571, p: non-significant)*

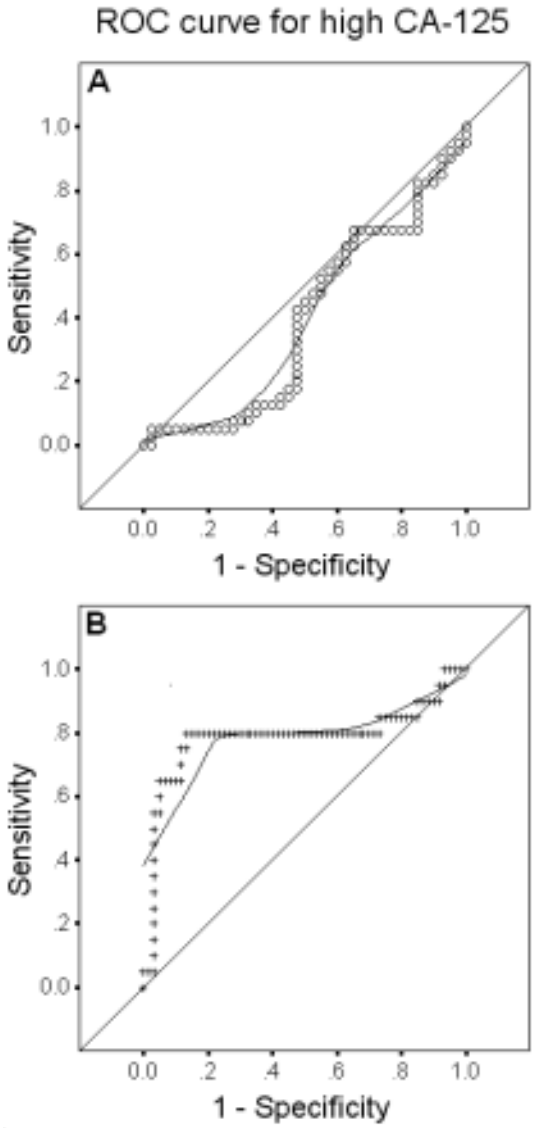

Figure 3. *Receiver Operator Characteristic (ROC) curves of high CA-125 levels as diagnostic tests for ectopic (A:?) or intrauterine abortive (B:+) gestation. The smallest cut-off value is the minimum observed test value minus 1 and the largest cut-off value is the maximum observed test value plus 1. All the other cut-off values are the averages of two consecutive ordered observed test values. The diagonal line with slope of one (AUC = 0.5) represents the theoretical test of no discriminatory value.* $AUC_{ectopic}$ *= 0.394 (95% CI: 0.268-0.520, p: non-significant),* $AUC_{abortive}$ *= 0.788 (95% CI: 0.639-0.957, p<0.001)*

When using a progesterone concentration of less than 10.75 ng/ml as a cut-point for the diagnosis of EP, sensitivity, specificity, positive and negative predictive values were all 85% (95% CI: 70.9-92.9) (Table 2). When using a CA-125 concentration of more than 41.9 U/ml as a cutoff value for the diagnosis of intrauterine abortive pregnancy, sensitivity was 80% (95% CI: 58.4-91.9), specificity 86.7% (95% CI: 75.8-93.1), the positive predictive value was 66.7% (95% CI: 46.7-82.0) and the negative predictive value 92.9% (95% CI: 83.0-97.2) (Table 3).

Table 2. *Cross-tabs of women with ectopic, intrauterine abortive or normal pregnancy and progesterone levels above or below the value of 10.75 ng/ml* *

	Type of Pregnancy			
	Ectopic	Intrauterine abortive	Intrauterine normal	Total
Progesterone levels = 10.75 ng/ml	34	5	1	40
Progesterone levels > 10.75 ng/ml	6	15	19	40
Total	40	20	20	80

* Derived from ROC-analysis as a cut-off value of significant sensitivity and specificity

Discussion

For the preservation of the corpus luteum and adequate progesterone production a functional fetoplacental unit is required. Therefore, in the present study, progesterone levels in abnormal pregnancies were significantly decreased (Table 1, Figure 1A), which is in agreement with previous reports[4-19]. Since progesterone levels are correlated with the duration of pregnancy, adjustment for this parameter was performed. Progesterone concentrations have also been implemented as an index for selecting surgical vs. pharmaceutical (methotrexate) treatment of EP[33,34] and evaluating the therapeutic outcome[34,35]. This is also in accord with the present results, since progesterone levels were significantly decreased after effective surgical treatment (Table 1, Figure 1A).

There is much controversy, though, as to whether a single progesterone measurement can be helpful in the (differential) diagnosis of EP when clinical and sonographic findings are ambiguous. In our study, a satisfactory combination of specificity, sensitivity, positive and negative predictive values was observed. This finding is in agreement with the results published by Stern et al[17], whose cut-point at 5 weeks of gestation (10 ng/ml) was also very close to ours (10.74 ng/ml). Nevertheless, our results are also in contrast to those of others, who have demonstrated a significant overlap of values[5-7,20-22] especially between women with EP and IU abortion[5-7].

Furthermore, according to the only meta-analysis published so far[23], the discriminative capacity of a single progesterone measurement is relatively poor. Given the fact that cut-off values in the literature range from 5[5] to 40[8] ng/ml with contradictive results, we postulate that variations of the studied populations and the assays used make it quite unlikely that progesterone levels alone can be easily implemented as a diagnostic test of overall and definite value for the prediction of EP.

So far, few studies of CA-125 as a possible diagnostic marker of abnormal pregnancies have been published. To the best of our knowledge, in none of them were both women with EP and IU abortion compared to

Table 3. *Cross-tabs of women with ectopic, intrauterine abortive or normal pregnancy and CA-125 levels above or below the value of 41.9 U/ml**

	Type of Pregnancy			
	Ectopic	Intrauterine abortive	Intrauterine normal	Total
CA-125 levels = 41.9 U/ml	6	16	2	24
CA-125 levels < 41.9 U/ml	34	4	18	56
Total	40	20	20	80

* Derived from ROC-analysis as a cut-off value of significant sensitivity and specificity.

normal controls. In the present report, a significant increase of CA-125 levels in women with abortive pregnancy was observed (Table 1, Figure 1B), independent of pregnancy duration. This is in agreement with most acute studies, which have demonstrated increased concentrations of CA-125 when a miscarriage is pending[26-28].

This increase is, most probably, due to extensive destruction of decidual and mucosa epithelial cells, which have been known to express substantial levels of this marker. Therefore, CA-125 levels were significantly decreased in women with spontaneous abortion after surgical removal of necrotic tissue (Table 1, Figure 1B). It should be mentioned, though, that in another study, first trimester serum CA-125 levels have not been found to be of significant predictive value for future abortion[29].

With regard to EP, both increased[30] and reduced CA-125[31] have been reported, compared to normal controls. In our study, no significant difference between women with ectopic and normal pregnancy was found. Although destruction of tubal mucosa would be expected to increase the "leakage" of CA-125 from mucosal cells into maternal sera[30], impaired interaction between the ectopic trophoblast and tubal tissues could be responsible for the decrease in CA-125 levels observed by others[31]. With regard to the present observations, the interaction between these two mechanisms could account for the slight increase after surgery in the sub-group of women with EP (Table 1, Figure 1B).

Last but not least, it is very interesting that, by means of ROC analysis (Figure 3), the measurement of CA-125 levels was found to be a reliable test for discriminating spontaneous abortion from ectopic and normal pregnancies. Although the positive predictive value of a 41.9 cut-point (Table 3) was relatively low (66%), the diagnostic capacity in the exclusion of abortive gestation vs. tubal and normal IU pregnancy (negative predictive value) was intriguingly high (93%).

In summary, the present study confirms previous reports of decreased progesterone levels in EP and has demonstrated that CA-125 concentrations are significantly increased in spontaneous intrauterine abortions, compared to both ectopic and intrauterine normal pregnancies. For sure, the significant variance of serum concentrations limits our ability to draw firm conclusions and more prospective studies are needed. Still, we believe that measurement of progesterone and CA-125 levels in selected patients can be useful in discriminating ectopic pregnancy from intrauterine abortive or normal gestation.

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