

Receiver operator characteristics and diagnostic value of CA-125, progesterone, estradiol and β -hCG in the prediction of ectopic and abortive intrauterine gestations

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Abstract

Objective: The study was designed to investigate the predictive value of CA-125, progesterone, estradiol and β -hCG in the diagnosis of ectopic pregnancy (EP) and inevitable miscarriage. **Methods:** Forty women with EP, 17 with intrauterine (IU) abortive gestation and 24 regular pregnant women (controls) were studied. : Serum levels of CA-125, progesterone, estradiol and β -HCG were measured by Enzyme Linked Immuno Sorbent Assay (ELISA) techniques in 40 symptomatic women with ectopic pregnancy, 17 with intrauterine (IU) abortive gestation and 24 regular pregnant women (controls) during gestational age between (4-12) weeks at Al-Kadhmiya Teaching Hospital, Baghdad, Iraq, between November 2010 and June 2011. **Results:** Women with EP had significantly lower CA-125, progesterone, estradiol and β -HCG concentrations, compared to both women with IU abortive pregnancy and controls. When using CA-125 concentration of 25.5 U/ml as a threshold for the diagnosis of ectopic pregnancy, sensitivity was 75.7%, specificity 100%, the positive predictive value was 100% and the negative predictive value 71.4%. When using a progesterone concentration of 5 ng/ml as a cut-point for the diagnosis of EP, sensitivity, specificity, positive and negative predictive values were 86.8%, 100%, 100%, 80%, respectively. **Conclusion:** These results by using ROC curves. The measurement of CA-125 and progesterone levels is useful in discriminating ectopic and intrauterine abortive from normal gestations.

Key words: Cancer Antigen -125(CA-125), Progesterone, Beta subunit of Human Chorionic Gonadotropin (β HCG), Estradiol, Ectopic pregnancy, Normal intrauterine pregnancy.

Introduction

Ectopic pregnancy, the implantation of a fertilized ovum outside the endometrial cavity, ¹continues to be a major cause of maternal morbidity and responsible for 6% of pregnancy deaths.² CA-125 is a glycoprotein antigen commonly expressed by ovarian serous adenocarcinoma. Serum levels of CA-125 are used for monitoring the response to therapy in women with this cancer^{3,4}. It is also commonly elevated in non-malignant pelvic conditions including endometriosis, leiomyomas, and pelvic inflammatory disease and pregnancy. It has

been reported that the elevation of CA-125 level was observed in the first trimester and also immediately postpartum. The fetal chorion, amniotic fluid and maternal deciduas contain significant amounts of CA 125 and represent potential sources of the elevated serum levels of the protein in pregnancy.^{3,4}

The aim of our study was to investigate the predictive power of maternal serum levels of CA-125, P, and E2 for prediction of EP from normal intrauterine pregnancies.

Distinguishing normal from abnormal pregnancies is a clinical challenge because there is no definitive noninvasive diagnostic test available before visualization on ultrasonography. Clinicians must therefore follow patients over the course of several days to weeks for diagnosis^{1,11} a time in which there is some potential for the ectopic pregnancy to rupture and result in life-threatening intra-abdominal hemorrhage. Early treatment may also allow for tubal-conserving procedures to be used, which is important for a patient's future fertility.^{12,13} Therefore, development of a serum test to diagnose an ectopic pregnancy with high accuracy would be of great clinical significance. The diagnosis of ectopic pregnancy in early pregnancy requires both superior sensitivity and specificity given that a false-negative could lead to serious morbidity.

Methods:

Forty women with ectopic pregnancy (EP) gestational age 6.425 ± 0.142 and 24 women with normal IU gestation (controls) gestational age 5.54 ± 0.399 were studied. Serum samples from all 64 women were collected from Al-Kadhmiya Teaching Hospital, Baghdad, Iraq, between November 2010 and June 2011.

Diagnosis of ectopic pregnancy was based on clinical assessment and transvaginal ultrasonography (U/S). All EP were treated with laparoscopic salpingectomy. All women included in the control group eventually gave birth to healthy live borns and did not undergo any gestational complication.

From all women, blood was drawn by routine venipuncture. Blood samples were centrifuged at 3000 rpm and serum was stored at $-20\text{ }^{\circ}\text{C}$.

Results:

The basic anthropometric and clinical parameters of the women studied are presented in table 1. No significant difference in age, gestational age and body mass index (BMI) was observed between women with EP and women with normal IU gestation.

The concentrations of CA-125, progesterone, estradiol, and β -hCG, of the women studied are summarized in table 2.

CA-125 levels were significantly lower in the group of women with EP compared to women with controls ($P < 0.005$).

The ROC curves demonstrated a significant discriminatory ability of decreased CA-125 levels for the diagnosis of ectopic pregnancy. The AUC for CA-125 was 0.913 (95% CI: 0.841–0.984). A significant difference was found in EP ($P < 0.001$) table 3.

When using a CA-125 concentration of 20.5 U/ml as a cut-off value for the diagnosis of ectopic pregnancy from control groups, sensitivity was 75.5%, specificity 100%, the positive predictive value was 100% and the negative predictive value 71.4%.

Progesterone levels were significantly lower in women with EP, compared to woman with normal pregnancy ($P < 0.00001$).

Receiver operating characteristics analyses showed that progesterone value can be used for the differential diagnosis of EP from, with the areas under the curve being 0.979 (95%CI: 0.950-1.007). A significant difference was found in EP ($P < 0.001$) table 3.

The threshold for progesterone to differentiate ectopic pregnancy from normal ones was 5ng/ml, with a sensitivity of 86.8% and specificity of 100%, the positive predictive value was 100% and the negative predictive value 80%.

Estradiol levels were significantly lower in women with EP, compared to normal pregnancy ($P < 0.00$).

The ROC curves demonstrated a significant discriminatory ability of decreased estradiol levels for the diagnosis of ectopic pregnancy. The AUC for estradiol was 0.971 (95%CI: 0.935–1.006). A significant difference was found in EP ($P < 0.001$) table 3.

When using estradiol concentration of 27.5pg/ml as a cut-off value for the diagnosis of ectopic pregnancy from control groups, sensitivity was 83.8%, specificity 100%, the positive predictive value was 100% and the negative predictive value 75%.

The β -hCG levels were significantly lower in EP compared normal pregnancies ($P < 0.000$).

The ROC curves demonstrated a significant discriminatory ability of decreased β -hCG levels for the diagnosis of ectopic pregnancy. The AUC for β -hCG was 0.943 (95%CI: 0.88–1.000). A significant difference was found in EP ($P < 0.001$) table 3.

When using β -hCG concentration of 104.5 mIU/ml as a cut-off value for the diagnosis of ectopic pregnancy from control groups, sensitivity was 75%, specificity 100%, the positive predictive value was 100% and the negative predictive value 86%.

Table 1: Basic anthropometric and clinical parameters of the women studied; (mean \pm SEM [minimum-maximum]).

	Type of pregnancy		
	Ectopic (n = 40)	IU normal (n = 24)	P-value
Age (y)	28.97 \pm 0.957 (18-45)	25.8 \pm 1.139 (18 - 3)	0.2
BMI (kg/m ²)	26.27 \pm 0.735 (18.2- 33.3)	24.98 \pm 1.278 (19 – 34.6)	0.3
Weeks of pregnancy	6.425 \pm 0.142 (4 - 8)	5.54 \pm 0.399 (4 – 10)	0.4

Table 2: CA-125, progesterone and estradiol, β -hCG levels of the women studied [mean \pm SER. (minimum–maximum)].

	Ectopic (n = 40)	IU normal (n = 24)	P-value
CA-125 (U/ml)	16.51± 2.39 (2-80)	74.25±18.5 (28-200)	<0.005
Progesterone (ng/ml)	2.54±0.47 (1-10.3)	28.36±3.7 (8-50)	<0.00
Estradiol (pg/ml)	13.4±2.14 (1-36)	112.7±23.6 (30-410)	<0.00
hCG (mIU/mL)	72.75±12.27 (5 - 200)	249.54±18.008 (105 – 300)	<0.00

Table 3: AUC for ROC analysis of different parameters with testing for statistical differences.

	AUC ± SEM	95% CI	P value
CA-125	0.913±.036	0.841-0.984	<.001
Progesterone	0.979±.015	0.950-1.007	<.001
Estradiol	0.971±.018	0.935-1.006	<.001
B-HCG	0.943±.029	0.887-1.000	<.001

Discussion

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 the germinal epithelium of the ovaries¹⁵. The fetal chorion, amniotic fluid, and maternal decidua also have been shown to contain significant amounts of CA-125 protein¹⁶.

In our study, The CA-125 in EP have been found lower than that in the normal pregnancy (P<0.005).

The low CA-125 levels in EP were explained by the impaired interaction between the fetal trophoblast and tubal mucosa⁴.

The results of our study are similar with Kobayashi *et al.* who found that serum CA-125 levels are high in women with normal early pregnancy, spontaneous abortion, and hydatiform mole, but they are low in women with tubal pregnancy, especially if there has been no uterine bleeding¹⁷.

Nevertheless, some studies showed that serum CA 125 measurements failed to discriminate between EP, and normal pregnancy. Schmidt *et al.* They concluded that single serum measurements of CA 125 in symptomatic first trimester pregnant patients failed to discriminate between spontaneous abortion, ectopic, and normal pregnancies.²

According to the results of this study, significant differences between serum β HCG levels in case and control group were noticed ($p < 0.00$). The specificity and sensitivity of single HCG measurement in detection of ectopic pregnancy at the cut-off level of 104 mIU/ml were 100% and 85% respectively. Although about 85% of women with ectopic pregnancy have serum HCG levels lower than those seen in normal pregnancy at a similar age. However a single quantitative HCG assay cannot be used for diagnosis of ectopic pregnancy because the actual dates of ovulation and conception are not known for most women.

In these cases the measurement of serum progesterone is helpful.

In this study, we found progesterone levels to be significantly lower in the EP ($P < 0.00$) than in the NIUP group.

The corpus luteum of women also secretes oestradiol (E2) in response to hCG and again could function as a luteal marker of pregnancy dynamics.

In our study, we found that the mean levels of E2 were significantly lower in the ectopic pregnancy patients than in NIUP ($P < 0.00$).

According to our findings, the measurement of CA-125 levels have value and specific in the differential diagnosis of ectopic pregnancy and early normal intrauterine pregnancy (the sensitivity of the test, according to cut-off 20.5 value, was 75.7%, specificity 100%, PPV 100%, NPV 71.4%).

In our study, we concluded that the single measurement of progesterone and estradiol measurement is useful to differentiate normal pregnancies from abnormal ones (EP).

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خاصية العامل المستلم وقيم CA-125 و β -hCG والبروجستيرون والاستراديول و في التنبؤ بالحمل والاسقاط لمريضات الحمل خارج الرحم

الخلاصة

و الاستراديول ال الأهداف: استكشاف القيمة التشخيصية لمستويات β -hCG وهرمون ال Progesterone و ال CA-125 في التشخيص المبكر لحمل خارج الرحم.

و ال الطريقة: تم قياس مستويات β -hCG وهرمون ال Progesterone وال CA-125 أليلايزا بواسطة تقنيه (لأربعين امرأة مصابه بالحمل خارج الرحم و24 امرأة سليمة بحمل طبيعي داخل الرحم ويعمر حمل (ELISA) الاستراديول يتراوح بين 4 و10 أسابيع ، تمت الدراسة في مستشفى الكاظمية التعليمي بغداد- العراق خلال الفترة بين نوفمبر 2010 و يونيو 2011.

النتائج: أشارت الدراسة إلى وجود انخفاض معنوي ملحوظ في قيم الاستراديول و ال β -hCG وهرمون ال Progesterone و ال CA-125 ($P \leq 0.05$) في أمصال الدم للنساء المصابات بالحمل خارج الرحم وكانت القيم كالتالي: $6.51 \pm 2.39 \text{U/ml}$; $2.54 \pm 0.47 \text{ng/ml}$; $72.75 \pm 12.27 \text{mIU/ml}$; $13.4 \pm 2.14 \text{pg/ml}$: السليمات ذوات الحمل الطبيعي داخل الرحم والتي كانت قيم المتوسط الحسابي \pm الخطأ المعياري للمتوسط الحسابي (Mean \pm SEM) كالتالي: $74.25 \pm 18.5 \text{U/ml}$; $28.36 \pm 3.7 \text{ng/ml}$; $249.54 \pm 18.0 \text{mIU/ml}$; $112.7 \pm 23.6 \text{pg/ml}$ على التوالي. وعند استخدام ال CA-125 و بتركيز 20.5U/ml كمستوى فاصل (Cut-off value) لتشخيص حالات الحمل خارج الرحم ، كانت الأنتقائية 75.7% وبحساسية مقدارها 100% وكانت القيمة التنبؤية الأيجابية 100% و السلبية 71.7% .

الختامه: أثبتت هذه الدراسة و باستخدام منحنيات ال ROC ، أن مستويات ال CA-125 وهرمون ال Progesterone (ألقياس لمرة واحدة) مفيدة في التشخيص المبكر لحالات الحمل خارج الرحم.