

Maternal Creatine Kinase is Not a Reliable Diagnostic Marker for Ectopic Pregnancy

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OBJECTIVE: To evaluate the efficacy and reliability of maternal serum creatine kinase (CK) as a diagnostic marker for ectopic pregnancy.

STUDY DESIGN: A total of 168 patients were included in this prospective study. Patients were divided into three groups. Group A consisted of 68 women presenting with possible ectopic pregnancy. Group B consisted of 50 women with normal intrauterine pregnancies and group C consisted of 50 cases with missed abortions matched for gestational age. Patients having a diagnosis of recent major trauma, noro-muscular system disorder, thyroid disorder or heart disease were excluded. Blood samples were obtained for CK, beta-human chorionic gonadotropin (beta-hCG) and progesterone measurements on admission and a transvaginal sonogram was performed prior to surgical intervention. Data were compared between groups using receiver operating characteristic (ROC) curve and one-way ANOVA with Tukey's post test.

RESULTS: While mean serum CK levels were higher ($p < 0.0001$), serum beta-hCG and progesterone levels were found to be lower in ectopic pregnancies ($p < 0.0001$ and $p < 0.0001$; respectively) relative to missed abortions and normal pregnancies. Receiver operating characteristic (ROC) curve analysis revealed an area under the curve of 0.715 for CK, 0.914 for beta-hCG and 0.961 for progesterone. A CK value > 45 IU/L was 60.3% sensitive and 77.8% specific, a beta-hCG value < 4229 mIU/mL was 100% sensitive and 75% specific and a progesterone value < 5.7 ng/mL was 100% sensitive and 79.4% specific in the diagnosis of ectopic pregnancy.

CONCLUSION: Although the mean value of serum CK is statistically significantly higher in ectopic pregnancy relative to controls, the positive predictive value and the sensitivity of CK is poor to allow CK to be a useful screening tool, comparing to beta-hCG and progesterone.

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Key Words: Creatine kinase, Ectopic pregnancy, Diagnosis

Ectopic pregnancy is one of the leading causes of maternal morbidity and mortality. Early diagnosis of ectopic pregnancy reduces the adverse outcomes associated with this disorder and has been made possible by the highly sensitive rapid beta-hCG assay, development of ultrasonography and diagnostic laparoscopy.

In recent years, it has been reported that elevation in creatine kinase may be used as an indicator of ectopic pregnancy as a consequence of trophoblast invasion of the smooth muscle layer of the Fallopian tube.¹ However, these findings could not be reproduced by most subsequent reports,²⁻⁴ while few other studies, which found similarly higher CK levels in ectopic pregnancy, also pointed out significant overlap with controls.⁵⁻⁶

In this study, in the view of controversial reports, we attempt to verify this observation and establish the sensitivity and positive predictive value of CK, to be a diagnostic marker for ectopic pregnancy.

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27

Materials and Methods

A total of 168 women were included in this prospective study. All patients enrolled in the study were divided into 3 groups. Group A consisted of 68 women presenting with suspected tubal ectopic pregnancy. Group B consisted of 50 women with normal intrauterine pregnancies and group C consisted of 50 cases with missed abortions matched for gestational age.

Patients with a history of recent major trauma, noro-muscular system disorder, thyroid disorder or heart disease were excluded from the study. The study was approved by the local ethics committee.

All the study and control subjects had a complete physical examination, routine blood tests and a pelvic ultrasound scan utilizing an ATL HDI 3000 ultrasound system (ATL Ultrasound Inc. WA; USA) with a 6.5 MHz transvaginal transducer. Patients with no visible intrauterine pregnancy who in addition demonstrate either an adnexal mass or cul-de-sac fluid were considered in the high risk group. A single echogenic ring surrounding either an intraendometrial fluid collection or the more echogenic deeper layer of decidua "surrounding" the less echogenic superficial layer detected by endovaginal sonogram was called pseudogestational sac and it was considered as a reliable indicator of ectopic pregnancy when a true "double decidual sac" (DDS) sign could not be demonstrated.

Table 1. Demographic variables of the study population

	Ectopic pregnancy (n=68)	Missed abortion (n=45)	Normal pregnancy (n=50)	Statistical significance (p)
Age	29.73±6.02	27.15±6.9	28.39±6.71	0.11
Gestational age	7.16±2.03	7.13±1.97	7.68±2.11	0.30
No. of pregnancy	3.39±2.27	2.97±2.39	3.04±2.47	0.58
Parity	1.22±0.95	1.15±0.88	1.18±0.92	0.92
D&Cs	0.79±0.66	0.56±0.45	0.48±0.81	0.03*
Abortions	0.25±0.32	0.35±0.28	0.31±0.27	0.19

† Presented as mean±standard deviation, *One-way ANOVA with Tukey's post hoc test

Table 2. Comparison between serum levels of CK, beta-hCG and progesterone

	Ectopic pregnancy (n=68)	Missed abortion (n=45)	Normal pregnancy (n=50)	Statistical significance (p)
Beta-hCG (mIU/mL)†	4788±8368	33071±5463	150826±116036	0.0001*
Progesterone (ng/mL)†	4.53±3.46	16.66±10.37	44.68±26.86	0.0001*
Creatine kinase (IU/L)†	65.4±82.92	37.7±11.26	38.6±14.22	0.0001*

† Presented as mean±standard deviation, *One-way ANOVA with Tukey's post hoc test

Blood samples were obtained for CK, beta-hCG and progesterone measurements on admission before any other procedure was performed. All tests for creatine kinase levels were performed on Biozyme CK-NAC (Biocon Diagnostics; Germany) slides, which measure creatine kinase activity by reflectance spectrophotometry. CK-MB was also performed on the samples utilizing CK-MB kits (BioSystems S.A. Costa Brava; Spain) to rule out a myocardial source for the elevated CK. Serum beta-hCG levels were determined by β -hCG Irma CT kits (Radim S.p.A. Pomezia; Italia), using fluorometric immunoassay and progesterone levels were determined by RIA progesterone kits (Beckman Coulter Co. Marseille; France).

Five of the samples in the missed abortion group showed elevation of CK-MB and were excluded from the study. After exclusions, all cases were further evaluated by clinical follow-up, laparoscopy or laparotomy. Tubal ectopic pregnancies were confirmed by surgical procedures and all cases were classified as ruptured or unruptured by visual examination during surgery and by subsequent histopathological evaluation.

Statistical analysis was performed using SPSS statistical software package version 10 for Windows (SPSS Inc. Chicago; USA). Creatine kinase, beta-hCG and progesterone levels in the three groups were compared by analysis of variance (ANOVA) with Tukey's test for post hoc comparisons. Statistical significance was set at $p < 0.05$. A receiver operating characteristic (ROC) curve was also constructed for the comparison of the three biochemical markers in the early diagnosis of the ectopic tubal pregnancy.

Results

Table 1 shows the demographics of the study population. There were no statistically significant differences between the

three groups regarding age, gestational age, total number of pregnancies and parity. The number of D&Cs were statistically significantly higher in ectopic pregnancy group than normal pregnancies and missed abortions ($p = 0.027$) (Table 1).

Comparison between serum levels of CK, beta-hCG and progesterone in the three groups are presented in Table 2. The mean level of maternal CK in women with tubal ectopic pregnancy was 65.40 ± 82.92 IU/L, significantly higher than the mean level in missed abortion (37.70 ± 11.26 IU/L; $p < 0.0001$) or normal pregnancy (38.60 ± 14.22 IU/L; $p < 0.0001$). No statistically significant difference was observed between CK levels of missed abortions, compared with normal pregnancies. The mean level of maternal serum CK in women with ruptured tubal ectopic pregnancy (125.1 ± 156.7 IU/L) was statistically significantly higher than those with unruptured ectopic pregnancies (47.03 ± 18.3 IU/L; $p < 0.001$). To rule out a cardiac source for the relative elevation of CK, the isoenzyme CK-MB was also determined. Five of the samples in the missed abortion group showed elevation of CK-MB and were excluded from the study.

The mean progesterone level in the ectopic pregnancy group was significantly lower than the levels in both missed abortion ($p < 0.01$) and normal pregnancy ($p < 0.001$) groups. The beta-hCG levels in normal pregnancies were significantly higher than the levels in both ectopic pregnancy ($p < 0.001$) and missed abortion ($p < 0.001$) groups. While serum beta-hCG levels were found to be lower in ectopic pregnancies (4788 ± 8368 mIU/mL) relative to missed abortions (33071 ± 54653 mIU/mL; $p > 0.05$) or normal pregnancies (150826 ± 116036 mIU/mL; $p < 0.001$), the difference was statistically significant only between ectopic pregnancy and normal pregnancy groups (Table 2). Beta-hCG levels were not statistically different between ectopic pregnancy and missed abortion groups ($p > 0.05$).

A receiver operating characteristic (ROC) curve was generated comparing CK, beta-hCG and progesterone for the early diagnosis of ectopic pregnancy (Figure I). ROC curve analysis revealed an area under the curve of 0.715 for CK, 0.914 for beta-hCG and 0.961 for progesterone. A CK value >45 IU/L was 60.3% sensitive and 77.8% specific, a beta-hCG value <4229 mIU/mL was 100% sensitive and 75% specific and a progesterone value <5.7 ng/mL was 100% sensitive and 79.4% specific in the diagnosis of ectopic pregnancy.

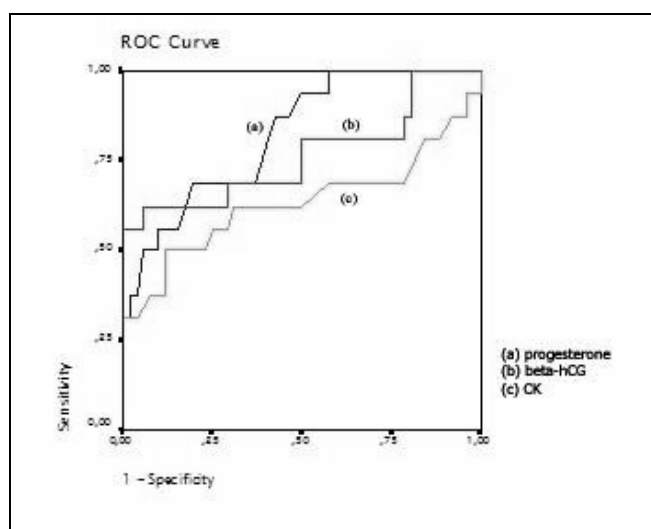


Figure I. ROC curve was generated comparing CK (c), beta-hCG (b) and progesterone (a) for the early diagnosis of ectopic pregnancy.

Discussion

Ectopic pregnancy is a life-threatening condition in which early diagnosis reduces the risk of maternal morbidity and mortality. Although, the most common screening for this condition involves the use of serum beta-hCG titers with transvaginal ultrasound,² these diagnostic tools may be insufficient in discriminating an early ectopic pregnancy from abnormal intrauterine or normal pregnancy. Recently, maternal serum progesterone and creatine kinase are used as other markers to identify patients at risk for possible ectopic pregnancy.^{1,7-9}

Serum creatine kinase is a product of muscle damage which has been suggested to be elevated in ectopic pregnancy as a result of invasion of the trophoblastic tissue into the muscular layer of the fallopian tube.¹ Although, this suggestion could not be reproduced by many subsequent reports,²⁻⁴ disagreement between these studies could arise from different selection criteria, as well as dissimilar control groups. In the present study, although the mean level of maternal CK in women with tubal ectopic pregnancy was significantly higher than the mean level in missed abortions or normal pregnancies, the distribution of values was too broad suggesting a significant overlap with the controls.

An acceptable cut-off value for serum creatine kinase in ectopic pregnancy is not yet available. Previous investigators have attempted to determine a serum CK breakpoint above which there is a high risk of ectopic pregnancy. Whereas in Lavie's study¹ a CK value of ≥ 45 IU/L was documented as highly diagnostic for ectopic pregnancy, Birkhahn et al.¹⁰ have advocated using a CK level <70 mIU/dL to rule out an ectopic pregnancy. We found that a serum CK value over 45 IU/L may predict a possible ectopic pregnancy, but do not have enough diagnostic power alone, since its sensitivity and positive predictive value is low.

Today, determination of serial beta-hCG with transvaginal ultrasound provides the widely accepted screening for a possible ectopic pregnancy. Hence, we compared CK with beta-hCG and progesterone to be a reliable predictor of ectopic pregnancy. According to our data, the positive predictive value and the sensitivity of CK was found to be lower when compared with beta-hCG and progesterone in the diagnosis of ectopic pregnancy. Although, serum beta-hCG still keeps its clinical importance in the diagnosis of ectopic pregnancy, determination of a single value is not helpful in ruling out the possibility of an ectopic pregnancy. Besides, we could not determine any cut-off value for beta-hCG to use in the evaluation of ectopic pregnancy.

Our data indicate that a serum progesterone value of 14 ng/mL is a critical threshold in discriminating abnormal from normal early pregnancy. In our study, no normal intrauterine pregnancies were determined below this value. The risk of an abnormal pregnancy was 84.1% in women who have a progesterone value below 14 ng/mL, but this threshold value could not predict an ectopic pregnancy.

In conclusion, more than one method have to be used in the diagnosis of ectopic pregnancy, as none of the above mentioned methods have enough diagnostic sufficiency alone in discriminating an ectopic pregnancy from early abnormal pregnancy. Serum CK may be helpful as an additional tool in the diagnosis of ectopic pregnancy, but it is not good enough to be used alone in clinical practice. Further studies are needed to evaluate the role of CK in discriminating ruptured from unruptured ectopic pregnancy.

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