Original Article

Role of creatine phosphokinase as a diagnostic marker in tubal ectopic pregnancy

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Abstract

Background and Aim: Ectopic pregnancy (EP) is still one of the leading preventable causes of maternal morbidity and mortality in the first trimester. Amidst the use of sensitive assays for β-HCG and high-definition ultrasonography for the identification of EP, the search for a more reliable and sensitive marker remains a challenge till date. Our aim was to determine the validity of creatine phosphokinase (CPK) and its isoenzyme (CPK-MB) in the prediction of tubal EP. **Materials and Methods:** A prospective and comparative diagnostic accuracy study was conducted among 105 pregnant women in the first trimester who met the eligibility criteria in the Department of Obstetrics and Gynecology, North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS). The study included 35 patients each with tubal EP (EP), abortive intrauterine pregnancy (AP), and normal intrauterine pregnancy (NP). CPK, CPK-MB, and β-HCG were measured among all the participants, and the participants were followed up longitudinally. **Results:** A total of 105 pregnant women were included. The mean CPK and CPK-MB levels were significantly higher among the women with EP when compared to NP ($P < 0.05$) and AP ($P < 0.05$) women; however, there was no significant difference between the NP and AP groups ($P > 0.05$). Moreover, the receiver operating characteristic (ROC) curve showed that both CPK and CPK-MB were good predictors of EP, with CPK (area under the curve [AUC] = 0.764) being a better predictor than CPK-MB (AUC: 0.650) in the diagnosis of EP. **Conclusion:** Early diagnosis of EP allows appropriate and timely management, which would not only reduce mortality and morbidity associated with the condition but also enable preservation of fertility and improve future pregnancy outcome. Hence, the need of the hour is a reliable biochemical diagnostic marker for EP, such as CPK.

Keywords: Creatine phosphokinase, diagnostic accuracy, ectopic pregnancy

Introduction

Ectopic pregnancy (EP) is a condition characterized by implantation of blastocyst outside the endometrium of the uterus. The most common site of extrauterine implantation is the fallopian tube, accounting for nearly 95% of cases.[1,2] It is one of the leading causes of pregnancy-related maternal deaths in the first trimester. Incidence varies between 0.25% and 1% of all pregnancies globally[2] and is 3.12/1000 pregnancies in India.[3] This small proportion accounts for 3% of pregnancy-related deaths.[1] Some developing countries such as Iran have ectopic-related maternal mortality as high as 10%.[4] Since 1960, a doubling in the prevalence of EP has been noted, accounting

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for 2% of the pregnancies in the first trimester. The incidence has also increased in recent years owing to increase in assisted reproductive technology, use of fertility drugs, intrauterine copper devices (IUCD) usage, increase in pelvic inflammatory diseases, and pelvic surgery.[2]

Currently, the common methods used for diagnosing EP are transvaginal ultrasound and serial human chorionic gonadotropin (β-hCG) assays. The classic triad of amenorrhea, abdominal pain, and vaginal bleeding with or without syncope is not always present. Despite the use of high-resolution transvaginal scans and sensitive assays for β -hCG, EP is still a diagnostic dilemma and challenge to the obstetricians, with 40%–50% of the cases being initially missed.[5] Misdiagnosis can lead to delay in treatment resulting in adverse maternal outcomes, thereby necessitating early and accurate diagnosis. Early identification of EP allows successful medical management, thereby obviating the need for surgical intervention and preventing the complications and long-term sequelae associated with it, thus once again reiterating the importance of timely diagnosis.

It has been reported in a recent series that most patients (48%–82%) presenting with classical triad have an equivocal ultrasound at quantitative β-hCG levels below the discriminatory zone (<1500 mIU/dL). This subgroup of patients may benefit the most from an additional diagnostic serum marker that is easily available and fairly reliable.[6] Hence, in our quest to find a diagnostic marker for EP, we studied the role of creatine phosphokinase (CPK).

In tubal pregnancies, the zygote lies next to the muscular layer due to the absence of submucosal layer in the fallopian tube. The trophoblast invades the muscle layer, causing smooth muscle injury and release of CPK into the circulation.[7,8] Lavie *et al.*[9] were the first to throw light into CPK as a possible serum marker in diagnosing EP, and it was concluded that it was both sensitive and specific in the prediction of tubal ectopic pregnancies.

Keeping in mind the importance of early diagnosis in reducing adverse maternal outcomes and the fact that diagnosis can be challenging despite the efficacy of serum β-hCG and vaginal ultrasonography, especially below the discriminative zone of β-hCG, and considering the cost of ultrasonography and serial β-hCG, which are expensive diagnostic tools compared to estimation of CPK, we determined the role of serum CPK as an early diagnostic marker for EP.

Materials and Methods

A prospective and comparative diagnostic accuracy study was conducted in the Department of Obstetrics and Gynecology, North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS), among the women who presented to the outpatient department and emergency room with complaints of amenorrhea, vaginal bleeding, and abdominal pain with or without syncope. Women with recent history of surgery, major trauma, chest pain, neurologic diseases, and recent history of multiple intramuscular injections were excluded from the study.

The study was approved by the institutional ethical committee (NEIGR/IEC/M13/F7/2020).

Sample size

The study included 35 patients each with tubal EP, abortive intrauterine pregnancy (incomplete/threatened/missed abortion), and normal intrauterine pregnancy, and hence, the included participants were divided into three groups as follows:

Group A: EP

Group B: abortive pregnancy (AP)

Group C: normal intrauterine pregnancy (NP).

Operational definition

EP was diagnosed in patients with pelvic pain, vaginal bleeding, or both and a plasma hCG level higher than 2000 IU/L without a sonographically visible intrauterine pregnancy or a combination of such a plasma hCG level with other sonographic signs such as an inhomogeneous adnexal mass or extrauterine gestational sac with or without cardiac activity.[10]

Study procedure

After obtaining informed consent form the study participants, all the enrolled patients were subjected to a detailed history and thorough clinical examination along with ultrasonography of pelvic organs. Before any invasive procedure, maternal venous samples were collected for total CPK, CPK-MB, β-HCG, in addition to other investigations required for surgical or medical intervention. CPK and CPK-MB levels were analyzed in an automated clinical chemistry analyzer AU 5800 (Beckman Coulter). The enrolled patients were followed up longitudinally.

Statistical analysis

Data was analyzed using Statistical Software Package for Social Sciences (IBM SPSS® V21). One-way analysis of variance (ANOVA) with Dunnett T3 post hoc analysis was used to determine the association of CPK and CPK-MB with the three groups (EP, AP, and NP). Receiver operating characteristic (ROC) curve was used to determine the predictive utility (area under the curve [AUC]) of CPK and CPK-MB in the diagnosis of EP. The diagnostic threshold (cut-off) was determined with Youden's index using the coordinates in the ROC. A P value of < 0.05 was considered statistically significant.

Results and Observations

In this study, a total of 105 patients were selected according to the inclusion and exclusion criteria and divided into three groups – EP,

AP and NP, each comprising 35 patients. The mean age of the study participants was 27.2 (4.9) years, with a minimum of 19 years and a maximum of 38 years. The mean period of gestation was 7.5 (2.5) weeks. The study groups were comparable in terms of age, parity, and period of gestation ($P > 0.05$) [Table 1].

Table 2 and Figure 1 show that the mean CPK values were higher in women with EP (mean CPK: 106.28) when compared to women with AP (mean CPK: 57.57) and NP (mean CPK: 54.65) and the difference was found to be statistically significant ($P < 0.001$). On post hoc analysis using Dunnett T3 test, there CPK values were significantly higher among women with EP when compared to NP ($P = 0.001$) and AP ($P = 0.002$) women; however, there was no significant difference between the NP and AP groups ($P = 0.936$).

Table 3 and Figure 2 show that the mean CPK-isoenzyme (CPK-MB) values were higher among women with EP (mean CPK-MB: 31.14) when compared to women with AP (mean CPK-MB: 21.94) and NP (mean CPK-MB: 18.09) and the difference was found to be statistically significant ($P = 0.001$). On post hoc analysis using Dunnett T3 test, the CPK-MB values were significantly higher among women with EP when compared to NP ($P = 0.03$) and AP ($P = 0.048$); however, there was no significant difference between the NP and AP groups ($P = 0.274$).

Table 4a and Figure 3 show that both CPK and CPK-MB were good predictors of EP and the ROC curve was found to be statistically significant ($P < 0.05$). However, CPK was found to be a better predictor of EP with an AUC of 0.764. The cut-off value for the prediction of EP with CPK was 63.0 with a sensitivity and specificity of 74%, whereas the cut-off value for the prediction of EP with CPK-MB was 26.5 with a sensitivity of 48.6% and specificity of 85.7%, as shown in Table 4b.

Discussion

EP is still one of the leading preventable causes of maternal morbidity and mortality in the first trimester. In addition, several studies have shown that the prevalence of EP is increasing in recent decades due to increased risk factors for EP, especially the use of assisted reproductive technology. On the other hand, the morbidity and mortality associated with EP have decreased due to the therapeutic transition from surgical emergency by laparotomy to conservative surgery by laparoscopy and medical therapy. Application of such conservative therapeutic modalities is possible only in early diagnosed patients with hemodynamically stable status. Despite the use of sensitive assays for β-HCG and high-definition transabdominal and vaginal ultrasound, it is believed that 40%–50% of EP cases remain unidentified in the early stages, particularly below the discriminative zone of β-hCG, thus posing a great diagnostic challenge.[5] It is also important to note the fact that almost half of the tubal pregnancies report when they have already ruptured,[11] thereby pointing the necessity for early detection to prevent fatal consequences and the requirement of a diagnostic

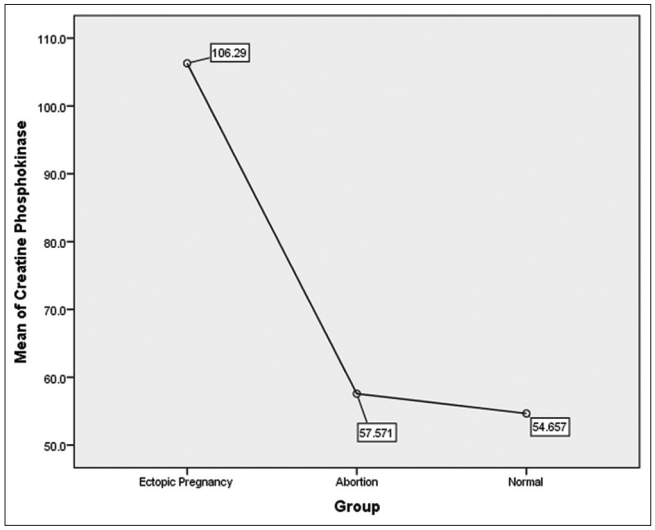

Figure 1: Mean plot showing the CPK values between the groups ($N = 105$). CPK = creatine phosphokinase

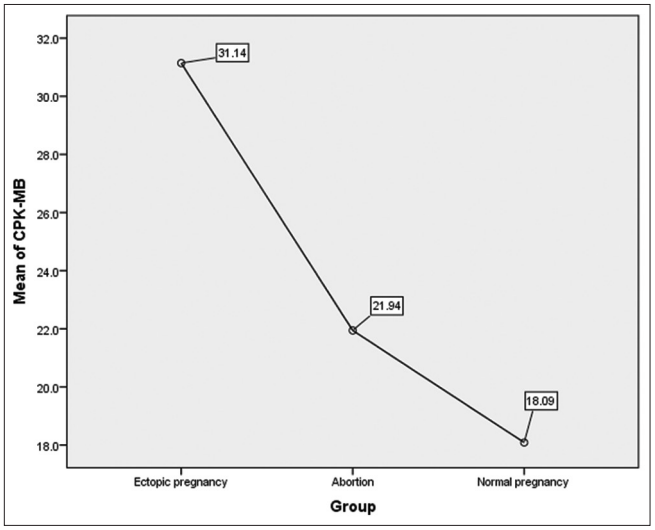

Figure 2: Mean plot showing the CPK-MB values between the groups ($N = 105$). PK-MB = creatine phosphokinase-isoenzyme MB

Table 1: Sociodemographic and obstetric characteristics of the study participants (n=105)

	Group A (EP) (n=35)	Group B (AP) (n=35)	Group C (NP) (n=35)	*P*
Age, Mean (SD)	27.9 (5.7)	27.2 (4.2)	26.5 (4.9)	0.491[a]
Period of gestation, Mean (SD)	6.3 (1.7)	8.3 (2.7)	7.9 (2.5)	0.08[a]
Parity				
Primi, *n* (%)	6 (17.1)	6 (17.1)	12 (34.3)	0.143
Multi	29 (82.9)	29 (82.9)	23 (65.7)	

ANOVA=analysis of variance, AP=abortive intrauterine pregnancy, EP=ectopic pregnancy, NP=normal pregnancy. [a]One-way ANOVA

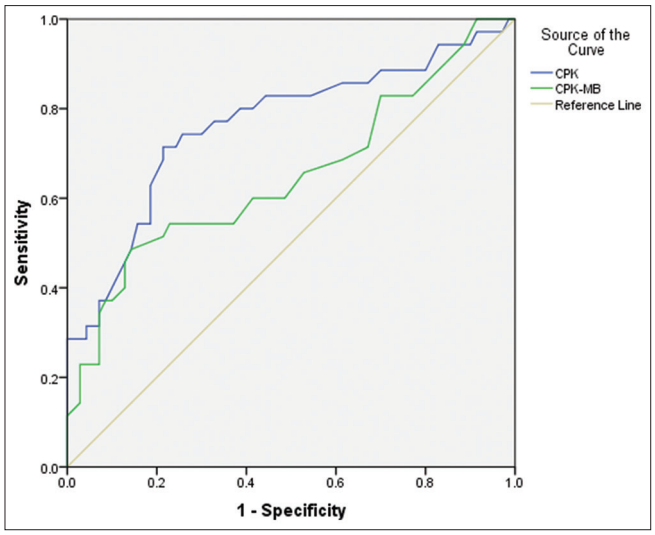

Figure 3: ROC curve for the prediction of ectopic pregnancy using CPK and CPK-MB (*N* = 105). CPK = creatine phosphokinase, CPK-MB = creatine phosphokinase-isoenzyme MB, ROC = receiver operating characteristic

marker with good accessibility and reliability to diagnose tubal EP at the earliest.

The present study included a total of 105 women divided into three groups, that is, EP, AP, and NP, consisting of 35 patients each. In our study, we found the mean CPK in EP group was higher with a value of 106.28 ± 75.1 U/L compared to AP and NP, which had values of 57.57 ± 23.8 and 54.65 ± 22.74 U/L, respectively. Similarly, the mean CPK-isoenzyme (CPK-MB) values were found to be higher among women with EP, who showed a mean value of 31.14U U/L, compared to women with AP and NP with mean CPK-MB values of 21.94 and 18.09 U/L, respectively. Our finding is comparable to that of Shafi *et al.*'s[12] study, where the mean CPK in EP was 97.64 ± 33.08 U/L and the mean CPK in the control group was 53.20 ± 9.75 U/L. Another study by Asgharnia *et al.*[2] in which CPK was compared in similar groups showed similar results: the mean CPK levels were 96.27 ± 63.9 U/L (EP), 55.37 ± 14.1 U/L (threatened abortion), and 48.94 ± 19.2 U/L (NP).[2,13]

A systemic review[14] evaluating 24 studies (from 1990 to 2018) conducted to study the role of CPK as a diagnostic marker for EP showed positive results regarding the use of CPK in EP diagnosis. In addition, the mean CPK level reported in this review was 95.02 ± 51.09 IU/L for EPs and 53.61 ± 19.15 IU/L for NPs/intrauterine pregnancies, which is similar to the findings in our study.

In one-way ANOVA test, the mean levels of total CPK and CPK-MB were significantly higher in EP compared to other groups ($P < 0.001$). Similar findings were echoed by Ganta *et al.*,[5] where the mean CPK was found to be significantly higher in EPs in comparison to AP and intrauterine pregnancies. Several

Table 2: Association of CPK values between the groups (*n*=105)

Group	CPK		*P*[a]
	Mean	SD	
Ectopic pregnancy (*n*=35)	106.3	75.1	<0.001
Abortive pregnancy (*n*=35)	57.6	23.8	
Normal intrauterine pregnancy (*n*=35)	54.6	22.7	

ANOVA=analysis of variance, CPK=creatine phosphokinase, SD=standard deviation. [a]One-way ANOVA

Table 3: Association of CPK-MB values between the groups (*n*=105)

Group	CPK-MB		*P*[a]
	Mean	SD	
Ectopic pregnancy (*n*=35)	31.1	20.4	0.001
Abortive pregnancy (*n*=35)	21.9	10.7	
Normal intrauterine pregnancy (*n*=35)	18.1	8.6	

ANOVA=analysis of variance, CPK-MB=creatine phosphokinase-isoenzyme MB, SD=standard deviation. [a]One-way ANOVA

Table 4a: AUC for CPK and CPK-MB in the prediction of ectopic pregnancy (*n*=105)

Enzyme	AUC	95% CI	Standard error	*P*
CPK	0.764	0.660-0.869	0.053	<0.001
CPK-MB	0.650	0.531-0.770	0.061	0.012

AUC=area under the receiver operating characteristic curve, CI=confidence interval, CPK=creatine phosphokinase, CPK-MB=creatine phosphokinase-isoenzyme MB

Table 4b: Cut-off values for CPK and CPK-MB for the prediction of ectopic pregnancy (*n*=105)

Enzyme	Cut-off value[a]	Sensitivity	Specificity
CPK	63.0	74.3	74.3
CPK-MB	26.5	48.6	85.7

CPK=creatine phosphokinase, CPK-MB=creatine phosphokinase-isoenzyme MB. [a]Based on the Youden's index (Youden's index=sensitivity + specificity−1)

studies such as those by Birkhahn *et al.*,[6] Kurzel *et al.*,[15] and Chandra and Jain[16] also reported significantly higher CPK level in the EP group.

In contrast, several studies such as those by Vitoratos *et al.*,[7] Kruchkovich *et al.*,[17] and Qasim *et al.*[18] reported no significant difference in total CPK and CPK-MB levels between groups. Most of these studies, however, are based on smaller study groups.

One possible explanation for the differing results could be the unsteady pattern followed by serum biomarkers over a normal gestation. Another explanation could be due to the artifact of different methods and the reagent used to detect them.

The ROC curve depicted that both CPK and CPK-MB were good predictors of EP and it was found to be statistically significant ($P < 0.05$). However, the AUC for CPK was higher (0.75) compared to the AUC for CPK-MB (0.65), making CPK a better predictor of EP.

In this regard, a few studies have reported the AUC as follows: Birkhahn *et al.*[19] 0.56, Soundravally *et al.*[20] 0.851, Ghahiri *et al.*[21] 0.692, and Shafi *et al.*[12] 0.985.The mean AUC of CPK was found to be 0.72 in diagnosing EPs according to these reported results, which is the same as that found in our study.

Our results show that serum CPK level can be used as an important tool in early diagnosis of tubal EP. Similar findings have been reported by several studies showing significant difference in CPK value between EP and intrauterine pregnancy and supporting the use of serum CPK measurement in diagnosis of tubal EP.[2,5,14,20,22-24]

In our study, we found maximum sensitivity (74.3%) and specificity (74.3%) for CPK occurring at a level of 63 IU/L. Similarly, the cut-off value for CPK-MB was found to be 26.5IU/L with a sensitivity of 48.6% and specificity of 85.7%. However, to determine the cut-off point with highest diagnostic sensitivity and specificity, large-scale prospective studies should be appropriately conducted.

Our study had certain limitations. The sample size of our study group was relatively small, and therefore, the power of the study could be less to comment on the statistical significance and hence its generalizabilty.

Nevertheless, results of our study will help health-care providers in the timely diagnosis and management of patients with EP and improve their outcome, thereby reducing the overall burden of EP. This can be achieved at the basic structural and functional unit of public health services. In a health-care system, the primary care providers (PCPs) are the ones that come in first contact with patients. With limited resources, the PCPs are at great disadvantage to arrive at correct diagnosis of certain health conditions, with EP being one of them as it closely mimics incomplete or missed abortion. Diagnosis of EP by β-hCG alone in the absence of sonography is challenging. In addition, at β-HCG levels below the discriminatory zone, even ultrasonography is equivocal. CPK can serve as an additional tool in overcoming this diagnostic dilemma. Use of CPK as a diagnostic marker will enable PCPs improve their ability to effectively manage patients with EP by early diagnosis and hence early treatment or referral when indicated. Our study will act as a facilitator and combat the health system barriers and enhance provision of effective care.

As the health-care system works to integrate primary care and public health, family physicians will have more opportunities to advocate for policies, resources, and interventions to positively impact medical and social outcomes of health and to align resources and focus their energies where they have the greatest impact.

Conclusion and Recommendations

Our study has reiterated the fact that early diagnosis of EP will allow not only prompt identification, but also appropriate management which would definitely reduce mortality and morbidity associated with the condition. Moreover, it will also enable preservation of fertility and improve future pregnancy outcomes by adoption of lesser-invasive management protocols.

Hence, the need of the hour is a reliable predictor. CPK may serve as an important tool in early diagnosis of tubal EPs. This is more relevant in low and middle income countries (LMICs) like India, where resources are scare and round-the-clock USG facilities are limited. CPK can be used as a reliable, readily available, expeditious, and cost-friendly diagnostic biochemical marker for EP. The results of our study highlight the potential benefits of CPK and CPK-MB as markers for early diagnosis of EP. However, the need for larger-scale studies was felt to appropriately determine the cut-off points of these markers.

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Conflicts of interest

There are no conflicts of interest.

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