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Evaluation of Maternal Serum Creatinine Phosphokinase (CPK) Level in Ectopic Pregnancy

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Abstract:

Background: Ectopic pregnancy is still an important cause of maternal mortality and morbidity in first trimester and early diagnoses of it can prevent a life threatening conditions. In ectopic pregnancy the fertilized egg lies next to the muscular layer of fallopian tube and this invasion causes an elevation of creatine phosphokinase (CPK) in blood.

Aim of the study: The current study aimed to evaluate the level of maternal serum Creatinine Phosphokinase (CPK) as a diagnostic method in detecting early ectopic pregnancy.

Methods: This cross sectional comparative two groups study was conducted at Maternity Teaching Hospital, Erbil City, Kurdistan Region, Iraq between September 2018 to September 2019. The study included two groups; group of 50 women with ectopic pregnancy and another group of 50 women of normal intrauterine pregnancy aged from 18 - 44 years. the level of Creatinine Phosphokinase (CPK) in serum, B-HCG level and vaginal ultrasonography were done in all in addition to the routine investigations.

Results: The mean CPK level in normal and ectopic pregnancy were 51.98 IU/L and 129.30 IU/L respectively. It is obvious that the CPK level is significantly higher in ectopic pregnancies. This study showed that $CPK \geq 70.9$ predicts ectopic pregnancy with Sensitivity: 86%, Specificity: 94%, the positive predictive value 93.5%, and the negative predictive value 87%

Conclusion: current study shows that maternal serum CPK levels are significantly higher in women with ectopic pregnancy. CPK can be used as adjuvant diagnosis of ectopic pregnancy.

Keywords: Ectopic Pregnancy, Creatinine Phosphokinase (CPK).

Introduction:

An ectopic pregnancy (EP) is a condition in which a fertilized egg implants in any location other than inside the uterine cavity (1). Ectopic pregnancy is often called tubal pregnancy because it most commonly occurs in a fallopian tube, however, it can also happen in ovaries, abdominal cavity, cervix and site of caesarean section scar (2). Early and accurate detection of an ectopic pregnancy is very important, because it can prevent a life-threatening condition and bringing down the maternal mortality and morbidity (3). According to (4) ectopic pregnancy accounts for approximately 2% of all pregnancies. Assisted reproductive, sterilization, pelvic infections, and IUCD usage are the main causes of recent increase in incidence of ectopic pregnancy.

Effective treatment of an ectopic pregnancy can help in saving the fallopian tube from permanent damage and preserve the chance of future fertility. Diagnosis of ectopic pregnancy is still presents challenges because the classic triad (Amenorrhea, abdominal pain and vaginal bleeding) is not always seen. This is in addition to the fact that the most common methods of diagnosis now a day such as vaginal sonography and serial beta-HCG level remain unable to diagnose all the cases of ectopic pregnancy (5), therefore, searching new methods of detection is vital. In ectopic pregnancy the trophoblast eroding into the muscle layer of fallopian tube that lacks a sub mucosal layer causes damage and releases muscle cell products such as Creatinine Phosphokinase CPK into the maternal circulation leading to elevation of CPK level (6). This being the case, the CPK level can serve as an effective diagnostic method in the early detection of ectopic pregnancy.

Methods

This was a cross sectional comparative two group study, conducted at Maternity Teaching Hospital, Erbil City, Kurdistan Region, Iraq between September 2018 to September 2019. The study was approved by Kurdistan Board of Medical Specialties (KBMS) ethical committee. The study included group of 50 women with ectopic pregnancy and another group of 50 women of normal intrauterine pregnancy aged from 18 - 44 years. All cases of ectopic pregnancy during this study,

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diagnosed based on clinical, biochemical and sonological criteria. Clinical features included amenorrhea, abdominal pain and vaginal bleeding with or without shock. Biochemical criteria were done by B-HCG level. Sonographic criteria include empty uterine cavity with adnexal mass, extra uterine gestational sac with or without free fluid in pouch of Douglas. The group of normal intrauterine pregnancy were the normal healthy patients that attended the outpatient clinic of the hospital with period of amenorrhea, without abdominal pain and vaginal bleeding. The normal intrauterine pregnancy confirmed by B-HCG level and transvaginal ultrasound. Exclusion criteria: Women with a recent history of surgery, major trauma, chest pain, neurological disease, heart disease, renal disease, myopathy, thyroid disease and recent history of multiple intramuscular injections were excluded.

After the informed consent were obtained a detailed history with thorough clinical examination along with routine investigations and ultrasonography of pelvic organs was done, followed by taking 2 milliliters of blood from women in early pregnancy (intra-uterine and ectopic) and sent to the laboratory to be centrifuged to extract plasma from the blood, then by especial kit using COBAS equipment within 13-15 minutes the level of Creatinine Phosphokinase (CPK) were determined in the plasma.

Statistical analysis

Data were analyzed using the statistical package for social sciences (SPSS, version 22). Frequencies and percentages were calculated. Chi square test of association was used to compare proportions. Student's t test of two independent samples was used to compare two means. McNemar test was used (in the 2X2 table) when the results of CPK were compared with the type of pregnancy (of the same patients); as in the following table:

		Pregnancy			P (By McNemar)
		Ectopic	Normal		
CPK	High	TP	FP	TP+FP	
	Low	FN	TN	FN+TN	
Total		TP+FN	FP+TN	Grand total	

TP=True positive; TN=True negative; FP=False positive; FN=False negative.

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Sensitivity = TP / (TP+FN)*100; *Specificity* = TN / (FP+TN)*100; *Predictive value positive (PV⁺)*: TP / (TP+FP) * 100; *Predictive value negative (PV⁻)*: TN / (FN+TN) * 100; *Total agreement* = (TP + TN) / Grand total.

A p value of ≤ 0.05 was considered as statistically significant.

Results

Hundred women were included in the study, 50 with normal pregnancy, and 50 with ectopic pregnancy. The mean age of the women with ectopic pregnancy (29.4 years) was significantly higher than the age (25.3 years) of women with normal pregnancy ($p < 0.001$) as presented in Table 1 which shows that 18% of the women of ectopic pregnancy aged ≥ 35 years, compared with 4% of women with normal pregnancy. Nearly all (96%) of the women with ectopic pregnancy were multiparous, compared with 68% of the women with normal pregnancy ($p < 0.001$). No significant difference was detected between the two groups regarding history of abnormal uterine bleeding ($p = 0.673$).

Table 1. Basic characteristics of the study sample by type of pregnancy.

	Normal pregnancy		Ectopic pregnancy		Total		
	No.	(%)	No.	(%)	No.	(%)	p
Age (years)							
< 25	24	(48.0)	9	(18.0)	33	(33.0)	
25-34	24	(48.0)	32	(64.0)	56	(56.0)	
≥ 35	2	(4.0)	9	(18.0)	11	(11.0)	0.002†
Mean (\pmSD)	25.3	(\pm 4.1)	29.4	(\pm 5.6)			<0.001*
Parity							
Primi	16	(32.0)	2	(4.0)	18	(18.0)	
Multi	34	(68.0)	48	(96.0)	82	(82.0)	<0.001†
History of abnormal uterine bleeding							
Yes	16	(32.0)	18	(36.0)	34	(34.0)	

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No	34	(68.0)	32	(64.0)	66	(66.0)	0.673†
Total	50	(100.0)	50	(100.0)	100	(100.0)	

*By t test for two independent samples. †By Chi square test.

The mean of CPK among women with ectopic pregnancy (129.30 U/L) was significantly ($p < 0.001$) higher than the mean (51.98 U/L) of CPK of women with normal pregnancy, as presented in Table 2. On the other hand, the mean of Beta HCG of women with normal pregnancy (4300.48 mIU/ml) was significantly ($p < 0.001$) higher than the mean (2045.62 mIU/ml) among women with ectopic pregnancy. Table 2 shows no significant differences between the two study groups regarding the means of weight, height, and gestational age.

Table 2. Means of the studied variables of the two study groups.

	Normal pregnancy		Ectopic pregnancy		p
	Mean	(±SD)	Mean	(±SD)	
Serum Creatinine Phosphokinase (CPK) U/L	51.98	(±14.03)	129.30	(±79.51)	< 0.001
B-HCG (mIU/ml)	4300.48	(±2098.53)	2045.62	(±1373.89)	< 0.001
Weight (Kg)	62.44	(±8.14)	63.84	(±9.37)	0.427
Height (Cm)	158.86	(±6.94)	158.72	(±5.12)	0.909
Gestational age (weeks)	6.14	(±1.64)	6.76	(±1.56)	0.056

Table 3 shows that the most common mode of presentation was amenorrhea (100%), then comes vaginal bleeding (78%), abdominal pain (70%), and shock (8%). The highest proportion (42%) of women were treated by laparotomy, and 38% by medical treatment.

Table 3. Mode of presentation and management of women with ectopic pregnancy.

	No.	% (n=50)
Mode of presentation*		
Amenorrhea	50	100.0
Vaginal bleeding	39	78.0
Abdominal pain	35	70.0
Shock	4	8.0

Management		
Laparotomy	21	42.0
Medical	19	38.0
Expectant	8	16.0
Laparoscopy	2	4.0

*Note: More than one mode of presentation may occur in the same woman.

Figure 1 and Table 4 shows that the area under the curve was 0.934, which was significantly ($p < 0.001$) different from the diagonal line (area of 0.50). The ROC curve had set the cut off value of CPK at 70.9 U/L.

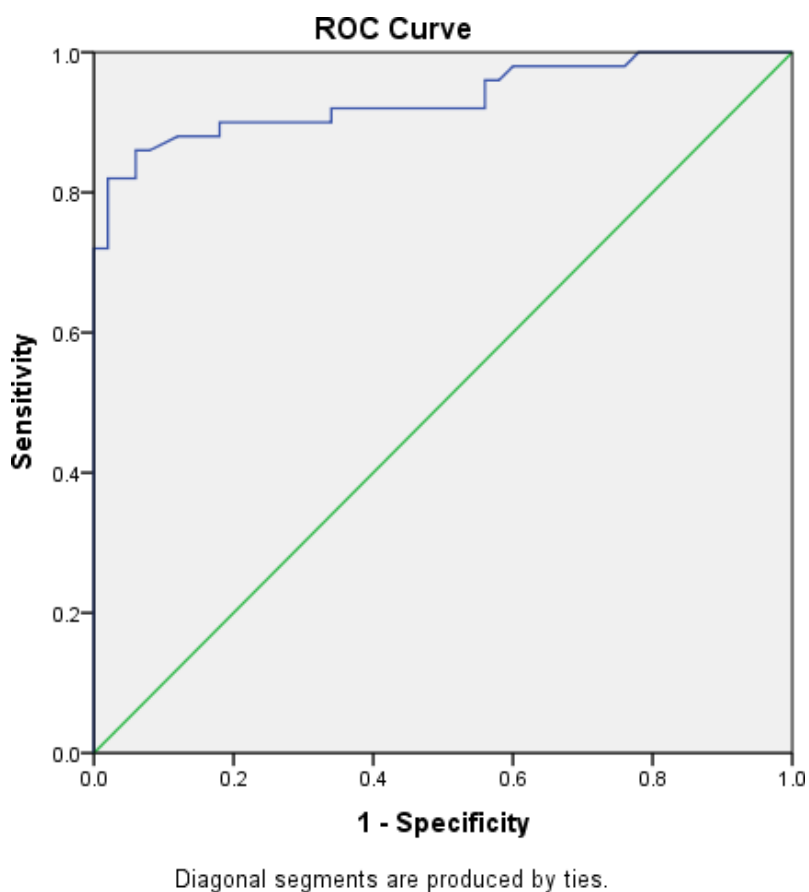


Figure 1. Receiver Operating Characteristics (ROC) curve of CPK as a predicting test for ectopic pregnancy.

Table 4. SPSS output for the area under the curve.

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Area	Std. Error	p value	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.934	0.026	< 0.001	0.882	0.985

Table 5 shows that all the accuracy indicators of CPK were high. The sensitivity was 86%, the specificity was 94%, the predictive value (PV) positive was 93.5%, and the PV negative was 87%. The total agreement rate was 90%. No significant ($p = 0.344$) difference was detected between the CPK level (as a screening test) and the real outcome. Accordingly, CPK can be considered as a good predictor of ectopic pregnancy.

Table 5. Accuracy of CPK in predicting the ectopic pregnancy.

Pregnancy				
CPK (U/L)	Ectopic	Normal	Total	p (McNemar)
High (≥ 70.9)	43	3	46	0.344
Low (< 70.9)	7	47	54	
Total	50	50	100	
Sensitivity	Specificity	PV+	PV-	Agreement%
86%	94%	93.5%	87%	90%

Discussion

Ectopic pregnancy is a relatively common complication in early pregnancy which causes major maternal morbidity and mortality with pregnancy loss and it is generally on the increase worldwide (7, 8). According to Elson et al (9) the incidence of ectopic pregnancy is approximately 11/1000 pregnancies. From what have been mentioned, it is important to have reliable predictors in diagnosis of ectopic pregnancy.

The present study included a total of 100 women divided into two groups: group of 50 women with ectopic pregnancy and another group of 50 women of normal intrauterine pregnancy aged from 18 - 44 years. The level of Creatinine Phosphokinase (CPK) in serum in addition to B-HCG level and vaginal ultrasonography were done in all.

In current study the mean of CPK levels among women with ectopic pregnancy (129.30 ± 79.51 U/L) were significantly ($p < 0.001$) higher than the mean (51.98 ± 14.03 U/L) of CPK levels of women with normal pregnancy. This is comparable to Wazir et al (6) study where the mean CPK in ectopic pregnancies was 103 ± 50.3 U/L and the mean CPK in the normal pregnancy group was (52.4 ± 10.9 U/L). The result of this study also comparable to the study by Asgharnia et al (10) where the mean CPK levels in ectopic pregnancy were 96.27 ± 63.9 U/L and the mean CPK levels in the normal pregnancy were 48.94 ± 19.2 U/L. There are more studies found that the CPK levels of ectopic pregnancy to be significantly higher than the normal pregnancy for example Ganta et al (5), Lavie et al (11) and Shafi et al (12).

Current study showed that $CPK \geq 70.9$ predicts ectopic pregnancy with Sensitivity: 86%, Specificity: 94%, the positive predictive value 93.5%, and the negative predictive value 87%., This is well agree with Wazir et al (6) study that reported the serum CPK level of 70 U/L with sensitivity 95%, specificity 98%, the positive predictive value 99% and the negative predictive value 90.7% for the diagnosis of ectopic pregnancy. Accordingly, the CPK levels can be considered as a good predictor of ectopic pregnancy.

Conclusion

Current study shows that maternal serum CPK levels among women with ectopic pregnancy are significantly higher than the maternal serum CPK levels of women with normal pregnancy. Hence, it may serve as an important adjuvant in the diagnosis of ectopic pregnancy along with the available methods such as β -hCG and Transvaginal ultrasound. According to the present research work the serum CPK level of ≥ 70.9 U/L may be useful as a predictor of ectopic pregnancy.

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