

Reliability of Maternal Serum Creatine Kinase in Diagnosis of Tubal Pregnancy

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Abstract

Objective(s): To assess the reliability of maternal serum creatine kinase in diagnosis of tubal pregnancy and to look for the clinical and laboratory parameters in these patients.

Method(s): Maternal venous blood was taken for estimation of serum creatine kinase before any invasive procedure. Creatine kinase level was detected by UV kinetic method-NAC activated. The correlation of CPK levels in patients with tubal pregnancy and controls with normal intrauterine pregnancy was done. Logistic regression analysis and ROC curve analysis have been used to analyse the data.

Result(s): CPK levels were significantly higher in all patients in study group than in control group. We found maximal sensitivity (97%) and specificity (98.7%) for CPK occurring at a cut-off level of > 69.2 IU/L.

Conclusion(s): CPK level of >69.2 IU/l serves as an important tool in diagnosis of tubal pregnancy.

I. Introduction

Ectopic pregnancy is the most common cause of pregnancy related mortality in the first trimester.¹⁻³

The egg settles in the fallopian tube more than 95% of the time. This is why ectopic pregnancies are commonly called tubal pregnancies. The egg can also implant in the ovary, abdomen or the cervix. None of these areas has much space or nurturing tissue as uterus for a pregnancy to develop. As the fetus grows it will eventually burst the organ that contains it. This can cause severe bleeding and endanger the mother's life.⁴

A large portion of the current pool of literature is directed towards early identification of ectopic pregnancy when successful medical management can obviate the need for surgical intervention. Tubal sparing techniques such as methotrexate, salpingostomy, salpingotomy are more successful when used early in gestation. These techniques have been reported to be more likely to decrease the morbidity associated with ectopic pregnancy when compared with laparotomy and salpingectomy.⁵ For reducing maternal mortality and morbidity early diagnosis is critical.^{6,7} Early diagnosis of first trimester hemorrhage presents an important challenge.⁸

Transvaginal ultrasound and serial β -hCG determination are currently the most common methods used for diagnosis.⁹⁻¹² Despite the use of high resolution transvaginal sonography and sensitive assays for β -hCG, it is believed that 40 to 50% of cases are initially misdiagnosed.¹³ Serum β -hCG measurements can distinguish a normal intrauterine pregnancy (IUP) from a non-viable pregnancy but cannot distinguish arrested IUP from EP.^{10,12,14,15} In fact despite the advances in ultrasound a recent series reported that 48-82% of all patients presenting with abdominal pain and/or vaginal bleeding in the first trimester had an indeterminate ultrasound when the quantitative β -hCG was below 1000 mIU/dl. This subgroup of patients in particular cannot be accurately evaluated and may benefit most from a serum marker that is rapidly available and useful in the early diagnosis of tubal pregnancy.¹⁶ The lack of a submucosal layer in the fallopian tube allows the zygote to penetrate the epithelium and the trophoblast usually invades the muscle layer allowing muscle cell products such as creatine kinase to enter the circulation leading to increased serum CK levels during EP.¹⁷

Keeping in view that early diagnosis is critical for reducing maternal mortality and morbidity and the fact that despite the efficacy of serum β -hCG and vaginal ultrasonography, diagnosis can be uncertain below the discriminative zone of β -hCG and comparing the cost of ultrasonography and serial β -hCG which are expensive diagnostic tools in comparison to creatine kinase estimation, led us to study the role of serum creatine kinase as an early diagnostic marker for ectopic pregnancy. This study was conducted to see the reliability of maternal serum creatine kinase in diagnosis of tubal pregnancy and to look for the clinical and laboratory parameters in these patients.

II. Material & Methods

The present study was a prospective case control study and was conducted on 175 patients divided into two groups, 100 as cases and 75 as controls. This study was conducted in the department of Obstetrics and Gynaecology, SKIMSSoura and SKIMS medical college hospital Bemina, Srinagar, J&K during a period of 24 months during September, 2012 to August, 2014.

Patients with history and physical examination suggestive of tubal pregnancy were selected as cases & patients attending antenatal clinic matched for age and gestational period and having confirmed intrauterine

pregnancy as controls. Women with history of heart disease, neurological disease, thyroid dysfunction, renal disease, myopathy, recent history of trauma, recent history of multiple intramuscular injections were excluded from the study.

A detailed history with thorough clinical examination along with routine investigations and ultrasonography of pelvic organs was done. History included amenorrhea, pelvic and abdominal pain, vaginal bleeding or spotting, vasomotor disturbances like vertigo or syncope. Examination included general physical examination, per abdominal examination including tenderness on palpation, distention and muscle guarding, per vaginal examination including cervical movement tenderness, fullness in posterior fornix, palpable adnexal mass on affected side.

About 2ml of maternal venous blood was taken for estimation of serum creatine kinase before any invasive procedure. Creatine kinase level was detected by UV kinetic method-NAC activated.

The standard statistical tests of the parametric category were used like student's independent t-test and for categorical variables the chi-square test and fisher's exact test were used to get the valid results. Also the standard statistical charts were used to represent the data. All the results so obtained were discussed on 5% level of significance i.e., $p < 0.05$ considered as significant. The spss v20 was used as a statistical software to analyse the data.

III. Results

In this study a total of 175 patients were selected according to the inclusion and exclusion criteria and divided into two groups, 100 as cases and 75 as controls.

Table 1. shows that 78 (78%) patients out of 100 cases were hemodynamically stable and 22 (22%) patients were unstable. Majority of the patients who were hemodynamically stable proved to be unruptured tubal pregnancy on laparoscopy or laparotomy (n=49, 62.83%) while as almost all the patients who showed hemodynamic instability had ruptured tubal pregnancy on laparoscopy or laparotomy (n=20, 90.90%).

Out of 100 patients in study group 69(69%) patients had per abdominal findings suggestive of peritonitis and 31(31%) patients did not show any sign of peritonitis. Out of the patients who showed features suggestive of peritonitis majority had ruptured tubal pregnancy (n=43, 62.32%).

Majority of the patients (83%) had per vaginal findings suggestive of ectopic i.e., palpable adnexal mass, cervical movement tenderness and fullness in pouch of douglas and out of them 54.22% showed ruptured tubal pregnancy and 45.78% had unruptured tubal pregnancy.

Table 2. shows that all the patients in the study group were anemic with hemoglobin level less than 11gm/dl. Majority of the patients 92(92%) had mild to moderate anemia (Hb 7-10.6gm/dl) and 8(8%) patients had severe anemia (Hb<7gm/dl). All the patients with severe anemia had ruptured tubal pregnancy.

Table 3. shows that 95% patients in study group showed positive pregnancy test while 5% had negative pregnancy test. Significant ultrasonographic findings suggestive of ectopic pregnancy was present in 96 patients out of 99 while in 3 patients USG was insignificant in picking up tubal pregnancy and in 1 patient USG was not done.

Table 1. Clinical examination in study group in relation to ruptured and unruptured tubal pregnancy

		Total n=100	Ruptured pregnancy (n=49)	Unruptured pregnancy (n=51)	Results
Hemodynamic status	Stable	78 (78%)	29 (37.17%)	49 (62.83%)	P < 0.001
	Unstable	22 (22%)	20 (90.90%)	2 (9.10%)	
P/A suggestive of peritonitis	Present	69 (69%)	43 (62.32%)	26 (37.68%)	P < 0.001
	Absent	31 (31%)	6 (19.35%)	25 (80.65%)	
P/V suggestive of ectopic	Present	83 (83%)	45 (54.22%)	38 (45.78%)	P = 0.021
	Absent	17 (17%)	4 (23.53%)	13 (76.47%)	

Table 2. Hemoglobin levels in relation to ruptured and unruptured tubal pregnancy

Hemoglobin gm/dl	n = 100	Ruptured tubal pregnancy n=49	Unruptured tubal pregnancy n=51	Results
7 - 10.6	92 (92%)	41 (44.56%)	51 (55.44%)	P = 0.002
< 7	8 (8%)	8 (100%)	0	

Table 3. Pregnancy test and ultrasonographic findings in study group

		N	%
Urine pregnancy test (n=100)	Positive	95	95%
	Negative	5	5%
USG(TAS/TVS) Suggestive of ectopic pregnancy (n=99)	Significant	96	96.97%
	Insignificant	3	3.03%

Table 4. shows that 96 patients in study group underwent laparoscopy/ Laparotomy and out of them 49 (51.04%) had ruptured tubal pregnancy and 47 (48.96%) had unruptured tubal pregnancy. In 4 patients no invasive procedure was done and they were managed conservatively with methotrexate therapy

Table 4. Laparoscopic/ laparotomy findings in study group

Laparoscopic/laparotomy findings(n=96)	N	%			
R u p t u r e d t u b a l pregnancy	49	51	1	0	4
U n r u p t u r e d t u b a l pregnancy	47	48	96	9	6

Table 5. shows that mean CPK in ruptured tubal pregnancy was 111.71±41.56 which was significantly higher than in unruptured tubal pregnancy (84.12±11.36).

Table 5. showing CPK level in ruptured and unruptured tubal pregnancy

C P K levels U/L	Minimum	Maximum	Mean	S D	Median	Result	
R u p t u r e d t u b a l Pregnancy(n=49)	7	43	50	111.71	41.56	104	P < 0.001
U n r u p t u r e d t u b a l Pregnancy(n=51)	5	01	12	84.12	11.36	84	

It was seen that in order to differentiate ruptured from unruptured tubal pregnancy the highest threshold was observed at a cut-off value of 92 U/L for CPK with sensitivity 77.6% and specificity 84.3%. The positive predictive value was 82.60 and negative predictive value was 79.63.

Figure 1. shows ROC curve, area under the curve was 86.4% (with 95% C.I =0.781-0.924).

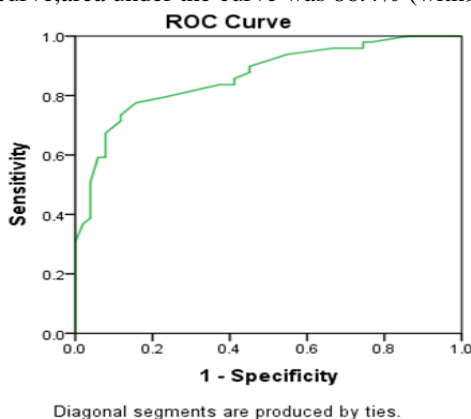


Figure 1. ROC curve

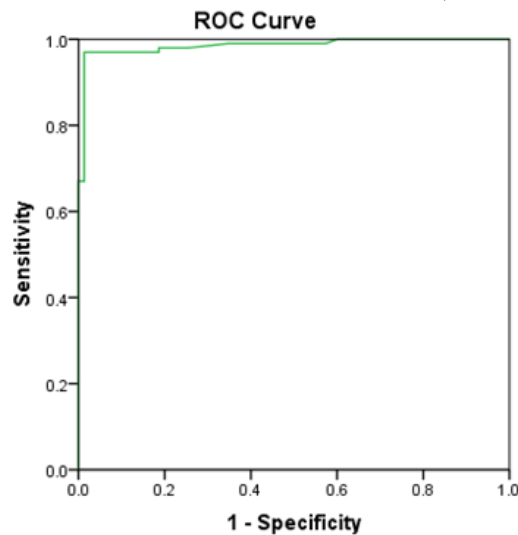
Table 6. shows that mean CPK in the study group was 97.64±33.08 which was significantly higher than in the control group (53.20±9.75).

Table 6. showing CPK level in study and control group

CPK level U/L	Minimum	Maximum	Mean	S D	Median	Results
Study group n=100	50	350	97.64	33.08	92	P < 0.001
Control group n=75	36	85	53.20	9.75	53	

In diagnosing tubal pregnancy the highest threshold was observed at a cut-off value of 69.2 U/L for CPK with sensitivity 97% and specificity 98.7%. The positive predictive value was 98.98 and negative predictive value was 96.10.

Figure 2. shows ROC curve, area under the curve was 0.985 (with 95% C.I= 0.954-0.997).



Diagonal segments are produced by ties.

Figure 2.ROC curve

IV. Discussion

Ectopic pregnancy is still the leading cause of pregnancy related maternal deaths in the first trimester.^{2,3,18} For reducing maternal mortality and morbidity early diagnosis is critical.^{6,7} Early diagnosis and management of first trimester hemorrhage presents an important challenge.⁸

This present study included 175 patients divided into two groups, 100 as cases with features suggestive of ectopic pregnancy and 75 as controls with normal intrauterine pregnancy.

In our study group majority of the patients (78%) were hemodynamically stable and most of them proved to be unruptured tubal pregnancy on laparoscopy or laparotomy (n=49, 62.83%) while as almost all the patients who showed hemodynamic instability had ruptured tubal pregnancy (n=20, 90.9%). There was no study available for comparison.

In study group majority (69%) of the patients had per abdominal findings suggestive of peritonitis. Majority of the patients with peritonitis had ruptured tubal pregnancy (n=43, 62.32%). There was no study available for comparison.

Majority of the patients (83%) had per vaginal findings suggestive of ectopic and out of them 54.22% showed ruptured tubal pregnancy and 45.78% had unruptured tubal pregnancy. There was no study available for comparison.

In the study group majority of the patients 92(92%) had mild to moderate anemia (Hb 7-10.6gm/dl) and 8(8%) patients had severe anemia (Hb<7gm/dl). All the patients with severe anemia had ruptured tubal pregnancy. There was no study available for comparison.

In our study group 95% patients showed positive pregnancy test while 5% had negative pregnancy test. Our study was comparable to the study done by Tumivaara on 552 cases in which 90% of the patients had positive pregnancy test.¹⁹

In our study group 96 patients out of 99 showed significant ultrasonographic findings suggestive of ectopic pregnancy i.e., adnexal mass, empty uterus with no gestational sac, fluid in pouch of Douglas, few patients had clear cut gestational sac and cardiac activity in the fallopian tube. In 3 patients USG was insignificant in picking up tubal pregnancy in whom tubal pregnancy was diagnosed on laparoscopy and in 1 patient USG was not done and she was also diagnosed as tubal pregnancy on laparoscopy. Beth C caplan in 1993 showed sensitivity of sonography 69% and specificity of 99% for detection of ectopic pregnancy.²¹

In our study group 96 patients had undergone laparoscopy/laparotomy and out of them 49 proved to have ruptured tubal pregnancy and 47 had unruptured tubal pregnancy. In 4 patients no invasive procedure was done and they were diagnosed as ectopic pregnancy on USG and serial β hCG levels and were managed conservatively with methotrexate therapy. There was no patient in our study with cervical, ovarian or abdominal pregnancy. Richard B. Kurzel in his study found all ectopic pregnancy as tubal pregnancy which was consistent with our study. In his study out of 33 patients 7 patients showed tubal rupture while as 26 patients had unruptured tubal pregnancy on laparoscopy.²²

In our study we found the mean creatine phosphokinase (CPK) in ruptured tubal pregnancy as 111.71 \pm 41.56 IU/L (range 74-350 IU/L) and in unruptured tubal pregnancy as 84.12 \pm 11.36 IU/L (range 50-112

IU/L). There was significant statistical correlation of CPK level with respect to ruptured tubal pregnancy ($p < 0.001$). Our study was consistent with the study done by Osman H. Develioglu et al. In his study he found mean CPK in ruptured tubal pregnancy as 152.1 ± 61.2 IU/L while in unruptured tubal pregnancy mean CPK was 91.6 ± 44.3 IU/L and concluded that serum CPK may help in discriminating ruptured from unruptured tubal pregnancy.²³ In our study in relation to ruptured and unruptured tubal pregnancy we found maximal sensitivity (77.6%) and specificity (84.3%) for CPK occurring at a cut-off level > 92 IU/L. Using this cut-off value positive predictive value of CPK was 82.60 and negative predictive value was 79.63 for diagnosing ruptured from unruptured tubal pregnancy.

In our study mean CPK level in the study group was 97.64 ± 33.08 IU/L (range 50-350 IU/L) where as mean CPK in the control group was 53.20 ± 9.75 IU/L (range 36.2-85 IU/L). There was significant statistical difference in CPK level between study and control group ($p < 0.001$). Our findings corroborate the observations made by Lavie et al²⁴, PK Saha²⁵, L Chandra¹⁷.

Lavie et al in his study found that serum CPK level was 45 IU/L in all patients with tubal pregnancy, significantly higher than the patients in control group and concluded that high serum creatine kinase level can be an important diagnostic test in evaluation of suspected tubal pregnancy.²⁴

PK Saha found that total serum CPK level to be significantly higher in the study group i.e., 34.15 ± 1.17 IU/L compared to the controls 18.72 ± 1.25 IU/L ($p = 0.001$) and concluded that when in doubt the test could be used as a marker for diagnosis of ectopic pregnancy.²⁵

L Chandra in his study found CPK level ≥ 75 IU/L in all patients with tubal pregnancy, which was significantly higher than in the controls ($p = 0.001$), thus concluded that maternal serum creatine kinase can be an important biochemical marker in suspected tubal pregnancy.¹⁷

In our study we found maximal sensitivity (97%) and specificity (98.7%) for CPK occurring at a level of > 69.2 IU/L. Using this cut-off value positive predictive value of CPK was 98.98 and negative predictive value was 96.10 for diagnosis of tubal pregnancy. By the ROC curve, area under the curve was 0.985 which shows that serum CPK level can be used as an important tool in diagnosing tubal pregnancy.

V. Conclusion

In our study CPK levels were significantly higher in all patients in study group than in control group. We found maximal sensitivity (97%) and specificity (98.7%) for CPK occurring at a cut-off level of > 69.2 IU/L. Using this cut-off value positive predictive value of CPK was 98.98 and negative predictive value was 96.10 for diagnosis of tubal pregnancy. As we know that early diagnosis is critical for reducing maternal mortality and morbidity and the fact that despite the efficacy of serum β -hCG and vaginal ultrasonography, diagnosis can be uncertain below the discriminative zone of β -hCG. Thus from the results obtained it is concluded that CPK level of > 69.2 IU/L serves as an important tool in diagnosis of tubal pregnancy.

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