Is Serum Creatine Kinase a Reliable Indicator for Early Diagnosis of Ectopic Pregnancy?

Parvin Mostafa-Gharabaghi, Seddigheh Abdollahi-Fard, Manizheh Mostafa-Gharabaghi, Nader Rashtchizadeh, Morteza Ghojazadeh, Arash Khaki, Elham Ghadamkheyre

ABSTRACT

Background: To determine the sensitivity of serum creatine kinase level in diagnosis of unruptured ectopic pregnancy. Methods: This descriptive prospective case control study was performed in Alzahra and Taleghani teaching hospitals in Tabriz Iran from 2006 to 2008 on 88 women with ectopic pregnancy (44 case of ruptured and 44 case of unruptured ectopic pregnancy). The control group was consisted of 44 women with normal intrauterine pregnancy. The serum creatine kinase level was measured by Eliza method in blood samples. Results: the results were compared by variance analysis and t-test. SPSS.14 statistical software were used for analyzing the data. By determining cut-off level of 45 Iu/L the specificity and sensitivity was estimated. The mean of creatine kinase level was 48.24±14.97 iu/l in intrauterine pregnancy and 54.40±20.40 iu/l and 87.00±45.42 iu/l in unruptured and ruptured ectopic pregnancies, respectively. The difference in creatine kinase level between ectopic pregnancy and normal intrauterine pregnancy was significant (p=0.001). The difference between serum creatine kinase level in rupture and unrupture ectopic pregnancy also was significant p=0.04. Creatine kinase levels above 45u/l was 65% sensitive and 79% specific for diagnosis of ectopic pregnancy from intrauterine pregnancy and 78% sensitive and 84% specific for diagnosis of unruptured ectopic pregnancy from ruptured ectopic pregnancy. Conclusions: Transvaginal sonography and quantitative bHCG measurement are the optimal and most effective strategy for diagnosis of ectopic pregnancy.

Key words: ruptured ectopic pregnancy, unruptured ectopic pregnancy, intrauterine pregnancy, serum creatine kinase.

Introduction

Ectopic pregnancy is a potentially life-threatening condition in which the fertilized egg implants outside the uterus. About 2 percent of all pregnancies is ectopic, it is the most common cause of pregnancy related mortality in the first trimester [5,2,6]. For reducing maternal mortality and morbidity, early...
diagnosis is critical [7,10]. It is possible by measurement of serum \( \beta \)HCG and vaginal ultrasonography [4,8]. Despite their efficacy, diagnosis can be uncertain below discriminative zone of \( \beta \)HCG.

Other new diagnostic markers are also described for diagnosis as progesterone, creatine kinase, CA125 and pregnancy specific \( \beta \) glycoprotein (PSBS)[5,6]. Measurement of serum levels of creatine kinase , an intracellular metabolic enzyme with high concentrations in the brain, the myocardium and skeletal and smooth muscle, have first been supported by lavie et al in ectopic pregnancy [3]. So far its measurement only been used in the evaluation of acute myocardial infarction [11].

In ectopic pregnancy the trophoblast can invade the muscular layer of the fallopian tube and the damaged muscle cells release creatine kinase in the maternal blood stream through the tubal blood vessels [12].

There is increasing concern that rising maternal creatine kinase activities could be an early biological index of tubal nidation, but there is no general agreement about using it [14].

The aim of this study was to determine the sensitivity and specificity of serum creatine kinase level in diagnosis of unruptured ectopic pregnancy.

**Methods:**

This descriptive study was carried out at Alzahra and Taleghani teaching hospitals in Tabriz,Iran from 2006 to 2008. The study group included 88 women from population of ectopic pregnancy who were admitted with signs and symptoms of ectopic pregnancy. Ectopic pregnancy was confirmed by laparoscopy or laparatomy in all cases.

The study group were divided into two groups ruptured(44 cases) and unruptured(44 cases) based on surgical findings.

The control group consist of 44 intrauterine pregnancies with similar gestational age, based on LMP and ultrasound findings who were randomly selected from population of normal pregnancy.

All study group gave informed consent to be included to study, which had been approved by Regional Research Ethics Committee.

Blood samples were obtained with consent, from all cases upon admission before any invasive procedure for the measurement of creatine kinase levels, another one just before surgery.

In control group the blood sample was obtained at the prenatal care clinic for measurement of creatin kinase.

Serum level of creatine kinase was measured by Eliza method (pars Azmon ck-203 kit made in Iran).

Sample size calculations, assuming 90% power, \( q=0.05 \) and \( p=0.5 \) indicated the need for at least 44 patients in each group.

Data management and analysis was performed using SPSS14.

Analysis of Variance (ANOVA) test was used to analyze the creatine kinase levels between three groups and chi –square test was used to compare differences between two groups.

Data were presented as mean\pm standard deviation. Significance levels were set at the \( p<0.05 \).

The efficiency and sensitivity of creatine kinase in prediction of ectopic pregnancy and differentiation of ruptured and unruptured ectopic pregnancy was estimated by ROC for determination of best cut off point.

**Results:**

Table 1 shows there was no significant differences in demographic characterstics of patients between two groups.

As shown in table 2 no significant difference was found in the site of ectopic pregnancy between two groups (\( p=0.83, \text{df}=1, x^2=0.046 \)).

Ampular pregnancy was the most common type of ectopic pregnancy.

As table 3 shows no significant difference was found in serum level of creatin kinase between normal intrauterine and ruptured ectopic pregnancies(\( p=0.998 \)) but it was significantly different between normal intrauterine and unruptured ectopic pregnancies(\( p=0.11 \))and also between ruptured and unruptured ectopic pregnancies(\( p=0.04 \)).

There was a significant difference in serum level of creatine kinase in diagnosis of unruptured ectopic pregnancy (Table 4). A significant difference was found in serum level of creatine kinase between ruptured(54.50\pm4.22) and unruptured (66.15\pm7.19) ectopic pregnancies in second measurement (\( p=0.04 \ r=0.72 \)).

The difference between ampular and isthmus pregnancies was significant (45.57\pm11.36 and 58.38\pm12.48 respectively, \( p=0.048 \)).

**Discussion:**

As mentioned in the literature review ,the diagnosis of ectopic pregnancy can be difficult because of the wide spectrum of clinical findings,from asymptomatic cases to acute abdomen and hemodynamic shock [5].

The findings from this study indicated that 15% of patients with ruptured ectopic pregnancy and 27.5% of unruptured cases were asymptomatic(\( p=0.45 \)).

The present study was designed to determine the sensitivity of serum creatine kinase level in diagnosis of unruptured ectopic pregnancy.

Gestational age as a determining factor for placental tissue volume, a known source of cratine kinase [13] was the same in all cases and control group (\( p=0.67 \)).
Table 1: Demographic characters of patients.

<table>
<thead>
<tr>
<th></th>
<th>Ectopic pregnancy (ruptured, unruptured)</th>
<th>Normal pregnancy</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>28.5±4.73 (18-40)</td>
<td>26.98±5.96 (16-40)</td>
<td>0.16</td>
</tr>
<tr>
<td>Gravid</td>
<td>1.99±0.77 (1-5)</td>
<td>1.78±0.57 (1-3)</td>
<td>0.12</td>
</tr>
<tr>
<td>Parity</td>
<td>0.86±0.09 (0-5)</td>
<td>0.68±0.11 (0-3)</td>
<td>0.33</td>
</tr>
<tr>
<td>Abortion</td>
<td>20%</td>
<td>30%</td>
<td>0.25</td>
</tr>
<tr>
<td>Number of abortion</td>
<td>0.35±0.06 (0-2)</td>
<td>0.33±0.10 (0-2)</td>
<td>0.83</td>
</tr>
<tr>
<td>Smoking</td>
<td>6.3%</td>
<td>5%</td>
<td>0.78</td>
</tr>
<tr>
<td>Gestational age</td>
<td>7.95±0.10 (6-10 weeks)</td>
<td>7.88±0.14 (6-10)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Table 2: Site of ectopic pregnancy.

<table>
<thead>
<tr>
<th></th>
<th>Ampula</th>
<th>Isthmus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruptured</td>
<td>82.4%</td>
<td>17.6%</td>
</tr>
<tr>
<td>Unruptured</td>
<td>80%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Table 3: Comparison of the serum level of βHCG in three groups.

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Lowest level</th>
<th>Highest level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal pregnancy</td>
<td>3515±2150.10</td>
<td>56</td>
<td>78689</td>
</tr>
<tr>
<td>Ruptured ectopic pregnancy</td>
<td>1016.9±142.58</td>
<td>44</td>
<td>2900</td>
</tr>
<tr>
<td>Unruptured ectopic pregnancy</td>
<td>1041.08±163.23</td>
<td>84</td>
<td>4987</td>
</tr>
</tbody>
</table>

Table 4: Comparison of the serum level of creatin kinase in three groups.

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Lowest level</th>
<th>Highest level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal intrauterine pregnancy</td>
<td>48.28±14.97</td>
<td>7</td>
<td>89</td>
</tr>
<tr>
<td>Ruptured ectopic pregnancy</td>
<td>54.40±20.40</td>
<td>19</td>
<td>107</td>
</tr>
<tr>
<td>Unruptured ectopic pregnancy</td>
<td>87±45.43</td>
<td>15</td>
<td>482</td>
</tr>
</tbody>
</table>

Table 5: Correlation between creatin kinase and βHCG.

<table>
<thead>
<tr>
<th></th>
<th>P</th>
<th>N</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrauterine pregnancy</td>
<td>0.21</td>
<td>44</td>
<td>0.2</td>
</tr>
<tr>
<td>Ruptured ectopic pregnancy</td>
<td>0.102</td>
<td>44</td>
<td>0.26</td>
</tr>
<tr>
<td>Unruptured ectopic pregnancy</td>
<td>0.84</td>
<td>44</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Lavie et al showed that serum creatine kinase would increase in ectopic pregnancy as a result of the trophoblastic invasion and ensuing damage to the muscularis layer of the tube [3,9]. They found creatine kinase level in all cases of ectopic pregnancy is higher than normal intrauterine pregnancies, and suggested that creatine kinase level is an useful diagnostic tool for diagnosis of ectopic pregnancy [3,9].

Though we did not find any significant difference of creatine kinase level between normal intrauterine pregnancy and ruptured ectopies (p=0.889) but the difference between normal intrauterine pregnancy and unruptured ectopic pregnancy was significant. The difference between ruptured and unruptured ectopic was significant (p=0.04). This result may be explained by the fact that half life of creatin kinase is short [1].

By determining the cut off level of 45 the sensitivity and specificity of creatine kinase measurement in diagnosis of ectopic and nonal intrauterine pregnancies was 65% and 79% respectively, while it was 78% and 84% in diagnosis of ruptured and unruptured ectopic pregnancies. This is the same as the results of Jenn Rene Zorn,s study.

Done on 20 cases of intrauterine and 14 cases of ectopic pregnancies and gaining 65% specificity and 50% sensitivity for creatine kinase in the diagnosis of ectopic pregnancy.

Osman, H. [11] estimated the sensitivity of 65% and specivity of 87% for creatine kinase by using cut off point of 120 iu/lit in the diagnosis of ruptured and unruptured ectopic pregnancies [3].

The current study found that the amount of creatine kinase in unruptured ectopic pregnancy was higher than ruptured. It seems possible that this result is due to muscular damage that precede rupture of the tube.

There was no correlation between the serum level of βHCG an indicator of the amount of viable trophoblastic tissue and creatin kinase in present study (Table 5). In second measurement the level of creatin kinase in ruptured ectopic pregnancy were lower than unruptured one. It may be due to short half-life of creatin kinase [1].

Another important finding was that the level of creatine kinase in isthmus ectopic pregnancy was higher than ampular (58.38±12.48 and 48.57±11.26 respectively) (p=0.48). The reason for this result is not clear but it may be due to more muscular damage in isthmus pregnancy.

Conclusions:

In conclusion, risk factors assessment and physical examination are the initial steps in the diagnosis of ectopic pregnancy. Transvaginal sonography and quantitative βHCG measurement are the optimal and most effective strategy for diagnosis. The findings of this study suggest a role for measurement of creatine kinase in differentiation of ruptured and unruptured ectopic pregnancies but not
for diagnosis. Further studies with more cases are therefore recommended.

References