Maternal Serum Creatine Kinase and Single Serum Progesterone Measurement as Predictors of Ectopic Pregnancy

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Abstract:

Objective: To evaluate the role of serum creatine kinase (CK) and progesterone (p) in the prediction of ectopic pregnancy (E.P).

Patients and methods: A prospective study was carried out on 60 pregnant women of comparable gestational age and they were divided into 3 groups: Group A: 20 patients with confirmed E.P. Group B: 20 patients with missed or spontaneous miscarriage. Group C: 20 women with normal intrauterine pregnancy (IUP). The following laboratory measurements were performed for the studied groups: 1- Test for serum CK level for all groups. 2- Test for serum progesterone for all groups. 3- Histopathological study to determine the depth of invasion of the trophoblast to the muscular layer of fallopian tube for group A.

Results: 1- The serum CK level was significantly higher in group A than in group B and C and was significantly higher in ruptured than in unruptured and in isthmic compared to ampullary EP. 2- The serum progesterone level was significantly lower in group A and B than in group C, but there was no significant difference between group A and B. 3- The serum progesterone level was significantly higher in ruptured than in unruptured EP. 4- There was significant positive correlation between serum CK and progesterone level in group A.

Conclusion: 1- An increase in serum CK levels probably antedates tubal rupture and could help in discriminating ruptured from unruptured EP. 2- Serum progesterone discriminates EP from normal IUP but it does not differentiate it from miscarriage. 3- The combination of both serum CK and progesterone in suspected EP has a higher differential accuracy than either analysis alone.

Keywords: Ectopic pregnancy, Creatine kinase, Progesterone.

Introduction:

Ectopic pregnancy (EP) is an unmitigated disaster of reproduction [(1)], where earlier diagnosis enhances both maternal survival and conservation of reproductive capacity [(2)] and it is defined as implantation of the conceptus in any site other than a normal intrauterine location [(3)].

The commonest site is in the tubes about (95%) the remainder may locate in the ovaries, broad ligament, and peritoneal cavity [(4)].

Seventy four percent of tubal pregnancies are situated in the ampulla, (12%) occur in the isthmus, (12%) are fimbrial and approximately (2%) are interstitial [(1, 2)].

A dramatic increase in incidence over time has been reported in several countries due to increased incidence of

salpingitis and increased use of intrauterine contraceptive devices (IUCDs) and assisted reproductive techniques [1, 2, 3].

The clinical features of ectopic pregnancy are not unique to the condition but the classic triad consists of amenorrhea, vaginal bleeding and abdominal pain [5, 6].

The conventional diagnostic means used are:

A- HCG level: HCG production in ectopic pregnancy is generally lower than in intrauterine pregnancy (IUP) [4] but the interpretation of a single result of HCG is difficult and usually needs serial HCG determination with at least 48 hour delay in making diagnosis [7, 8, 9], women with ectopic pregnancy have low HCG which may either decline slowly have a slow rise or plateau in comparison with normal intrauterine pregnancy [4].

B- Ultrasound (US): The detection of a normal IUP {at 4 weeks + 3 days by transvainal sonography (TVS)} virtually excludes the diagnosis of ectopic pregnancy [4] although a pseudogestational sac or decidual cast in ectopic pregnancy may be confused on US with an intrauterine sac [8].

The characteristic ultrasound features of ectopic pregnancy are [4]:

Empty uterus + adnexal sac + fluid in pauch of Dogllas (POD) [4] c-Laparoscopy [2, 10]. d-Culdocentesis: to exclude haemoperitonium [10].

Creatine Kinase (CK):

It is an intracellular metabolic enzyme with concentrations highest in the brain, myocardium, skeletal and smooth muscle [11, 12].

Creatine kinase and ectopic pregnancy:

In the pathogenesis of ectopic pregnancy the zygot penetrates the tubal epithelium, lying adjacent to the muscular layer and the trophoblast invades the muscular layer of the fallopian tube [13]. It has been hypothesized that one of the serum markers for tubal pregnancy could be an increase in the muscle cell product of CK released into the maternal blood stream after the cell damage, and maternal serum CK level can serve as an additional diagnostic tool in early diagnosis of ectopic pregnancy [14].

Progesterone:

It is the most important steroidal plasma hormone in human pregnancy [15, 16].

Serum progesterone measurement and ectopic pregnancy:

Serum progesterone value can often be to use to establish that there is an abnormal pregnancy, that is either a miscarriage or an ectopic pregnancy [1, 5] and the use of a single random level of progesterone, rather than serial measurement is because of that most investigators have failed to demonstrated a statistically significant increase of progesterone value over the first 10 weeks of pregnancy, a time when most ectopic pregnancy manifest [17, 18].

Patients and methods:

This study was conducted on 60 pregnant women age range between 18-40 years old in the University Hospital of Al-Nahrain College of Medicine/ Department of Gynecology and Obstetrics over a period of 14 months starting from the first of March, 2001 to the end of April 2002.

Women included in this study were divided into 3 groups:

Group A: 20 patients admitted to the hospital with positive pregnancy test

and symptoms or ultrasonographic findings suspicious of ectopic pregnancy confirmed by–surgical procedures (laproscopy and/ laprotomy) and histopathology.

Group B: 20 patients admitted to the hospital with non-continuing pregnancy (missed or spontaneous miscarriage) diagnosed by ultrasound or after curettage with comparable gestational age.

Group C: 20 women with normal intrauterine pregnancy of comparable gestational age as assessed by menstrual dates and confirmed by ultrasound scan.

Any women with history of recent trauma, surgery or intramuscular injection were excluded from the study. Women with history of muscle, heart, thyroid or liver disease, women with twin or multiple pregnancy and women who had taken exogenous progesterone or conceived after ovarian stimulation and all types of ectopic pregnancy other than tubal pregnancy were also excluded.

In addition to the routine laboratory tests, we performed the following laboratory measurements for them:

1- Test for measurement of CK level in the serum were performed to all groups upon admission, before any invasive procedure or intra muscular injection, by enzymatic calorimetric method using creatine kinase enzymatic calorimetric method kit from (RANDOX laboratories Ltd).

2- Test for the measurement of serum progesterone level for all groups by standard radio immunoassay technique using radio immunoassay kit from (CIS bio international).

Women with suspected ectopic pregnancy were followed during surgery and ectopic pregnancy confirmed and classified as ruptured or un ruptured tubal pregnancy, and were stratified by implantation site as isthmic or ampullary by visual examination intra operatively and subsequent histopathological study of the specimens taken, which also determined the depth of invasion of the trophoblast into the muscular layer of fallopian tube.

After that statistical analysis of the data was done to compare the level of serum CK and serum progesterone between the three groups of ectopic pregnancy, miscarriage and normal pregnancy.

The levels of CK and serum progesterone were also compared between ruptured and unruptured and between amplullay and isthmic ectopic pregnancy.

The statistical analysis of the data was performed using the following tests:

Modified student t-test, Chi-square test, Sperman's rank ordered correlation test.

Results:

After collection and categorization of the data from 60 women included in the study, statistical analysis was done and revealed the following:

(Table 1) show the characteristics of women with tubal pregnancy and control groups, the following results were noted:

1- The age range of presentation reflects that although the most likely age of the presentation with ectopic pregnancy was in the last 20s, women at either end of reproductive age spectrum are not exempt from developing ectopic pregnancy.

2- There was no statistically significant difference in age between women in the three studied groups (*P* value=0.85)

3- There was no statistically significant difference in weight between women in the three studied groups (*P* value=0.77)

4- There was no statistically significant difference in gestational age between women in the three studied groups *(P* value=0.7)

5- The incidence of ectopic pregnancy was more in multiparous women (80%) of the cases were multipara while (20%) were nulliparous)

6- There was no statistically significant difference between women in the three studied groups regarding history of previous preterm delivery or early spontaneous miscarriage.(*P* value=0.99)

7- Thirty- five percent of patient with ectopic pregnancy had history of using contraception previously. (20%) used intrauterine contraceptive device, (10%) used combined oral contraceptive pills and (5%) used barrier method (only one patient had ectopic pregnancy while using oral contraceptive pills)

8- History of previous abdominal surgery was identified in (30%) of cases with EP (10%) of them with caesarian section, (10%) with appendicectomy and (10%) with other abdominal surgery.

9- (80%) of patients in group A had history of pelvic inflammatory disease, which appears to be an important risk factor for development of ectopic pregnancy.

(Table 2) shows the number (%) and mean gestational age of ruptured and unruptured tubal pregnancy in group A. Sixty percent of them were ruptured while (40%) were unruptured, there was no statistically significant difference in the mean gestational age between women with ruptured and unruptured tubal pregnancy, although the mean gestational age in the unruptured was slightly lower.

(Table 3) show the number (%) of ampullary and isthmic pregnancy in group A. Most of the cases were ampullary in location (85%), while only (15%) of the cases were isthmic.

(Table 4) shows the number (%) of ruptured ectopic pregnancy in ampullary and isthmic pregnancy in group A. Fifty three percent of ampullary pregnancies found to be ruptured, while all isthmic pregnancy were ruptured (100%).

(Table 5) shows the mean serum CK level for the three compared groups. The mean serum CK level in group A was found to be significantly higher than in group B and C (*P* value <0.0001). A cut off value for serum CK of 125 IU/L was (100%) sensitive and specific for the diagnosis of ectopic pregnancy.

(Table 6) shows statistically significant difference in the mean serum CK level between ruptured and unruptured ectopic pregnancy being higher in the ruptured group (P<0.000 3). A cut off value for serum CK of 250 IU/L was (91.6%) sensitive and (78.5%) specific for the prediction of tubal rupture.

(Table 7) shows a statistically significant difference in the mean serum CK level between ampullary and isthmic ectopic pregnancy being higher in the isthmic group (P<0.007).

(Table 8) shows the mean serum progesterone level in the three compared groups.

The mean serum progesterone level in group A and B was significantly lower than in group C (P<0.0001) and lower in group B than in group A. but This difference was not statistically significant (P<0.18).

(Table 9) shows statistically significant difference in mean serum progesterone level between ruptured and unruptured ectopic pregnancy, being higher in the ruptured group (P<0.01).

(Table 10) shows the mean progesterone level in ampullary and isthmic ectopic pregnancy. The mean serum

progesterone level was higher isthmic than the ampullary group, yet the difference was not statistically significant (P<0.45).

(Figure 1) show a significant positive correlation between serum CK level and serum progesterone level in group A (correlation coefficient r=0.679).

Table (1): The characteristics of women with tubal pregnancy and control groups.

Characteristic	Group A no (%)	Group B no (%)	Group C no (%)
Age (Year)			
10-24	5 (25%)	4 (20%)	4 (20%)
25-30	10 (50%)	9 (45%)	11 (55%)
31-35	3 (15%)	3 (15%)	4 (20%)
>35	2 (10%)	4 (20%)	1 (5%)
Not significant *P* value=0.858			
Body weight (KG)			
40-50	3 (15%)	4 (20%)	2 (10%)
51-60	5 (25%)	6 (30%)	5 (25%)
>60	12 (6-%)	10 (50%)	13 (65%)
Not significant *P* value=0.772			
Gestational age (W)			
<6 W	4 (20%)	2 (10%)	2 (10%)
6-8 W	14 (70%)	14 (70%)	13 (65%)
>8 W	2 (10%)	4 (20%)	5 (25%)
Not significant *P* value =0.700			

Table (2): Number (%) and mean gestational age of ruptured and unruptured tubal pregnancies in group A.

	No.(%)	Mean gestational age (W)
Ruptured	12 (60%)	8
Unruptured	8 (40%)	6.5
Total	20 (100%)	

Table (3): No. (%) of ampullary and isthmic pregnancies in group A.

	No.	%
Ampullary	17	85
Isthmic	3	15
Total	20	100

Table (4): No. (%) of ruptured ectopic pregnancy in ampullary and isthmic pregnancies in group A.

	Ruptured No. (%)	Unruptured No. (%)	Total
Ampullary	9 (53%)	8 (47%)	17
Isthmic	3 (100%)		3
Total	12	8	20

Table (5): Mean serum CK level for all groups.

Mean serum CK level IU/L ± standard error		
A	B	C
302.37±23.6	80.56±5.3	96.38±5.0

Table (6): Mean serum CK level in ruptured and unruptured ectopic pregnancy.

Mean serum CK level IU/L± standard error		
	Ruptured	Unruptured
CK	359.90±90	203.59±14.28

Table (7): Mean serum CK level in ampullary and isthmic pregnancy.

Mean serum CK level IU/L± standard error		
	Ampullary	Isthmic
CK	278.36±22.88	438.42±28.78

Table (8): Mean serum progesterone level for all groups

Mean serum progesterone level ng/ml± standard error		
A	B	C
5.11±0.5	4.19±0.4	31.39±1.2

Table (9): Mean serum progesterone level in ruptured and unruptured ectopic pregnancy.

Mean serum progesterone level ng/ml± standard error		
	Ruptured	Unruptured
progesterone	6.14±0.65	3.59±0.67

Table (10): Mean serum progesterone level in ampullary and isthmic ectopic pregnancy.

Mean serum progesterone level ng/ml ± standard error		
	Ampullary	Isthmic
progesterone	4.84±0.55	6.63±1.91

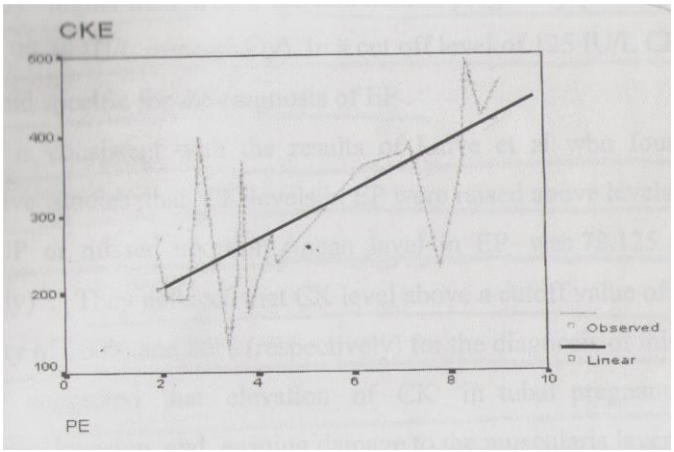

Figure (1): Regression curve estimation for correlation between serum CK level and serum progesterone level in group A.

Discussion:

*Serum CK level in ectopic pregnancy, abortion and normal pregnancy

In this study it was found that the mean serum CK level in ectopic pregnancy was significantly higher than in abortion and normal pregnancy (302.7 IU/L versus 80.56 and 96.38 IU/L respectively). In a cut off level of 125 IU/L CK was (100%) sensitive and specific for the diagnosis of ectopic pregnancy. This is consistent with the results of Laive et al who found in two consecutive studies that CK levels in ectopic pregnancy were raised above levels observed in normal intrauterine pregnancy or missed miscarriage. They deduced that CK level above a cut off value of 45 IU/L had a sensitivity & specificity of (100%) and (86%) respectively for the diagnosis of this condition. They suggested that elevation of CK in tubal pregnancy is due to trophoblastic invasion and ensuing damage to the muscularis layer of the tube, known to lack submucosal layer [14, 19]. These findings was supported by the studies of other authors who found that maternal serum CK can be an important biochemical marker in suspected tubal pregnancy [20, 21, 22, 23, 24]. However the difference in mean and cut off levels of CK measured in our study and these studies may be due to the difference in the method used for estimation of CK in the serum , difference in selection criteria of patient and the use of dissimilar control groups with different nutritional and genetic factors.

On the other hand the result of other studies doubt the described relationship between serum CK and the existence of ectopic pregnancy because the CK values found in tubal pregnancies in their studies were not statistically different from values obtained in control groups [25, 26, 27, 28, 29].

However the mean levels of CK in the control groups mentioned by Garcia-Velasco et al [25] were much higher than the mean levels of CK in the control groups of our study. What is striking also is that the findings of these authors could not be corroborated by the extent of tubal damage observed or by histologic evaluation of the involved tube which could influence the increase in CK levels.

*Serum CK level in ruptured and unruptured ectopic pregnancy

In our study (60%) of tubal pregnancies were ruptured. We found that CK level in ruptured ectopic pregnancy was significantly higher than in unruptured (359.9 IU/L versus 203.5 IU/L), however even in the unruptured group the CK level was significantly higher in comparison with abortion or normal pregnancy.

WE found that a cut off value for CK of 250 IU/L was (91.6%) sensitive and (87.5%) specific for the prediction of tubal rupture.

In the study of Develiglue et al (53%) of ectopic pregnancies were ruptured and they found that tubal rupture was associated with an increase in CK level while in unruptured ectopic pregnancy CK level may not necessarily differ from levels encountered in normal pregnancy. They revealed that the optimal cut off value of CK to be used for the prediction of tubal rupture in ectopic pregnancy was 120 IU/L which resulted in a sensitivity of (65%) and specificity of (87%) [30].

*CK level in ampullary and isthmic EP

In our study (85%) of tubal pregnancies were ampullary in location of which (53%) were ruptured and (15%) of the cases were isthmic in location all of which were ruptured. We found that the serum CK level in isthmic ectopic pregnancy is significantly higher than in ampullary EP (438.42 IU/L) versus (278.36 IU/L). This is inconsistent with the findings of Develiglue et al [30] and has been confirmed in more recent studies done by Soundravally et al and Abha et. al. [23, 31].

The presence of tubal rupture alone cannot account for the higher CK level observed in isthmic compared with ampullary ectopic pregnancy. Although the frequency of tubal rupture is admittedly higher in the isthmic ectopic pregnancy a significant difference in CK level between the two groups exist even when only ruptured cases of isthmic and ampullary ectopic pregnancy are considered, So the reason for the higher CK levels in the ruptured isthmic ectopic pregnancy compared with ruptured ampullary ectopic pregnancy could be a more extensive muscular damage at the time of invasion in the former.

Senterman et al have reasoned that the greater surface area of mucosa in the ampulla could favor intraluminal placental growth were as a relative lack of mucosa and the small caliber of the lumen could allow early invasion of the tubal wall in isthmic ectopic pregnancy [13].

*Serum progesterone in ectopic pregnancy, abortion and normal pregnancy

In our study progesterone level in ectopic pregnancy and abortion was significantly lower than in normal intrauterine pregnancy (5.1 ng /ml 4.1 ng/ml versus 31.3 ng/ml). There was no significance difference in progesterone level between ectopic pregnancy and abortion .No intrauterine pregnancy have progesterone level <20 ng/ml while no ectopic pregnancy have progesterone > 10ng/ml. It may be suggested that in ectopic pregnancy the fetoplacental unit appears to be dysfunctional presumably affected by the adverse condition at implantation site o of the fallopian tube and this is reflected by the uniformly low serum progesterone level.

This is consistent with the finding of Mathews et al and other authors who described different discriminatory levels for serum progesterone to distinguish viable intrauterine pregnancy from accidents of pregnancy (abortion and ectopic pregnancy) both individually and collectively but they could not efficiently discriminate abortion versus ectopic pregnancy [8, 32, 33, 34, 35]. They speculated that an active inhibitor or metabolic block for progesterone synthesis could be present in patient with ectopic pregnancy to cause decline in progesterone synthesis by corpus luteum [8].

Serum progesterone was also reported to be lower in ectopic pregnancy than in normal intrauterine pregnancy by other studies but there was significant overlap between values in both groups [36, 37, 38].

*Serum progesterone in ruptured and unruptured ectopic pregnancy

It was found that serum progesterone in ruptured ectopic pregnancy was significantly higher than in unruptured ectopic pregnancy. In the study of Hubinont et al (52%) of ectopic pregnancy were ruptured. A significant

positive correlation was present between B-HCG and serum progesterone. They concluded that the vitality of ectopic pregnancy that eventually ruptures is probably better than that of those do not rupture. This explains both the higher hormone secretion and the trophoblastic proliferation leading to tubal rupture [39]. Stovall et al findings in two different studies were consistent with these findings [10].

***Serum progesterone in ampullary and isthmic ectopic pregnancy**

Our study revealed that serum progesterone in the isthmic ectopic pregnancy was higher than in ampullary ectopic pregnancy, yet the difference was not statistically significant. There was no available study comparing serum progesterone level between ampullary and isthmic pregnancy.

***Correlation between serum CK and serum progesterone in ectopic pregnancy.**

Other finding in this study was the presence of significant positive correlation between serum CK and serum progesterone in ectopic pregnancy. The combined use of both assays in patients with suspected ectopic pregnancy may increase the proportion of cases in which adequate diagnosis can be established early and in which less invasive therapeutic approaches will be sufficient. Laive et al did not find such correlation in their studied groups [14].

Conclusion:

1-An increase in serum CK levels accompanying muscular damage in ectopic pregnancy antedates tubal rupture, and may be related to trophoblastic growth patterns.

2-Serum CK level is useful, rapid and easy test for early primary diagnosis of ectopic pregnancy, in addition it could help in discriminating ruptured from unruptured ectopic pregnancy.

3-Serum progesterone efficiently discriminate ectopic pregnancy from normal intrauterine pregnancy but it does not differentiate it from miscarriage.

4-The combined use of serum CK and serum progesterone measurement in patients with suspected ectopic pregnancy has a higher differential accuracy than either analysis alone.

Recommendation:

1- Serum CK and serum progesterone levels vary between laboratories and depend on the assay method used, so the clinician should be aware of the normal levels from laboratory at his institution before using the information clinically.

2- Serum CK and progesterone screening are advised to be widely employed in emergency department setting for patients at risk of ectopic pregnancy regardless of symptoms, and in any patient with risk factor if the diagnosis of ectopic pregnancy is being considered.

3- The combined use of serum CK and serum progesterone in the evaluation of patient at risk of ectopic pregnancy require further confirmation in a prospective trial before wide spread clinical implementation.

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