Experimental
&
Clinical Article

The Role of Beta-hCG Progesterone and Creatine Kinase in the Early Diagnosis of Ectopic Pregnancies

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OBJECTIVE: As ectopic pregnancy (EP) is an important cause that threatens life in the first trimester of pregnancy, the early diagnosis is important. The present study investigated the role of creatine kinase, progesterone and beta-hCG in the early diagnosis of EP.

STUDY DESIGN: Seventy-three patients admitted to Ankara Education and Research Hospital out-patient clinics. The patients were divided into three groups: Group 1; patients admitted to family planning unit for induced abortion (n=22), Group 2: patients diagnosed as spontaneous or missed abortion (n=23), Group 3; patients diagnosed as ectopic pregnancy (n=28). Serum samples were taken from patients for β-hCG, progesterone and creatine kinase before any management. SPSS for Windows 11,5was used for the analysis of the data.

RESULTS: Serum progesterone levels in normal pregnancies were statistically significantly higher than the levels in other two groups ($p<0.001$). But the progesterone levels in spontaneous abortion and ectopic pregnancy groups were not significantly different from each other. The best cut-off point for progesterone was determined as 14ng/ml with 94.1% specificity and 81.8% sensitivity. Serum β-hCG levels in normal pregnancy group were statistically significantly higher than abnormal pregnancies (missed, spontaneous abortion and ectopic pregnancy). The creatine kinase levels of the groups were not significantly different.

CONCLUSION: Serum biomarkers, β-hCG and progesterone are helpful for early diagnosis of abnormal pregnancy but could not be helpful to differentiate ectopic and abnormal intrauterine pregnancies. Creatine kinase is not helpful to differentiate EP and normal pregnancies.

Key Words: Ectopic pregnancy, Beta-hCG, Progesterone, Creatine kinase

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Introduction

An ectopic pregnancy (EP) is defined as the implantation and development of the gestational sac outside the uterine cavity, usually the adjacent site. The primary site in over 98% of ectopic pregnancies is the fallopian tube and the remainder EP's are located in the ovary, abdominal cavity, cervix or interstitium.[1]

The incidence of EP has been increasing in recent decades due to the growing number of risk factors e.g. high incidence of sexually transmitted disease, the use of assisted reproduction techniques, and the use of tubal sterilization and also due to increase in development in diagnostic methods.[2] Early diagnosis is difficult and longtime follow-up period may be necessary sometimes to differentiate EP from intrauterine pregnancy (IUP).

Since EP is one of the leading cause of maternal morbidity and mortality and preservation of fertility and tubal function is important in the management course, the early diagnosis is important. Usually transvaginal ultrasonography (TVS) and serum β-hCG levels are used for differential diagnosis of EP from IUP.[3,4] However, in the early pregnancy TVS and β-hCG cannot be sufficient to make true localization of pregnancy. For this reason, research is underway to identify serum biomarkers to help the diagnosis. In the literature, progesterone, creatine kinase (CK), Pregnancy-Associated Plasma Protein A(PAP-A), Human Placental Laktogen (HPL), Vascular Endothelial Growth Factor (VEGF), Glycodelin, Leukaemia Inhibiting Factor (LIF), Pregnancy Specific b1 Glycoprotein (SP1) are suggested to play important role in the early diagnosis of EP.[5,6]

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Creatine kinase (CK) is found in cell cytoplasm and mitochondria. In the case of cell injury, the energy production is diminished, cytosolic CK passes the cell membrane and the serum levels of CK increase. Mitochondrial CK is the definite indicator of cell death.[7] Due to the lack of submucosal layer in the fallopian tube, villous trophoblasts after invading the tubal epithelium lay on muscular layer in tubal pregnancies. The trophoblasts erode the blood vessels in the muscular layer and muscle cell product CK which enters the circulation. Therefore, the increase in serum CK is normal in EP and CK assay has been suggested for early diagnosis.[8]

Progesterone is synthesized from corpus luteum with the positive feedback of β-hCG from syncytiotrophoblast in the first 8-10 week of pregnancy and after that time synthesized from the placenta. Previous studies showed that progesterone levels are higher in normal IUP.[9,10] On the other hand, cut-off value of serum progesterone level (≤ 5 ng/ml) was suggested to be helpful to diagnose abnormal pregnancy but unable to discriminate between EP and unviable intrauterine pregnancy.[10]

The human chorionic gonadotropin (β-hCG) is a glycoprotein synthesized from syncytiotrophoblasts. The serum level increases in pregnancy and peak level is reached at 10 week of gestation. β-hCG level is most commonly used for the diagnosis of pregnancy. If the level is above the "discriminatory zone level" in which the gestational sac can be seen in the ultrasonography, a single β-hCG is diagnostic. But below this level serial β-hCG levels should be obtained for differential diagnosis, so the patients must be followed up for several days to weeks. This situation increases the anxiety of the patient and also the potential risk of life-threatening hemorrhage.[11]

As the early diagnosis of EP is important, in the present study we studied the efficacy of serum creatine kinase, progesterone and β-hCG levels as a biomarker in the diagnosis.

Material and Method

A total of 73 patients who admitted to Ankara Education and Research Hospital on July-November 2008 were included to study. The patients were divided into three groups; Group 1: pregnant who admitted to Family Planning Department for induced abortion (n=22), Group 2: patients with spontaneous abortion or missed abortion (n=23), Group 3: patients who had the diagnosis of ectopic pregnancy (n=28).

The patients in the groups were matched for age, gravid and gestational age. The diagnosis of ectopic pregnancies was made by surgery or dilation and curettage. Spontaneous abortion and missed abortion diagnosis were made by the observation of the fetoplacental material or serial β-hCG and USG follow-up and histopathological investigation after curettage. In Group 1 patients, ultrasonography was done to evaluate the localization of the fetus, fetal heart rate and gestational week.

Blood samples for β-hCG, progesterone and creatine kinase were taken from all patients before any medical or surgical treatment. Creatine kinase activity was determined by quantitative enzymatic colorimetric assay (Olympus, America, Inc.). The least value of CK by this assay was 3U/l. The serum progesterone was measured by chemiluminescence immunoassay quantitatively (Beckman Coulter Access®, Beckman Coulter Inc., Turkey). This test is competitively binding immunoenzymatic test. Chemiluminescence enzymatic immunoassay (Beckman Coulter Access®, Beckman Coulter Inc., Turkey) for quantitative determination of serum β- hCG was used.

Statistical Analysis

The data was analyzed by using SPSS for Windows 11,5. Descriptive statistics for continues variables were defined as median and standard deviation or mean (minimum-maximum). The difference in groups for the mean values of serum β-hCG, progesterone, and creatine kinase was tested by using Kruskal Wallis test. When the difference was significant with Kruskal Wallis test non parametric multiple comparing test was used to find out which group or groups make this significant difference. We used the area under the receiver operating characteristics (ROC) curve to investigate whether the serum progesterone values were diagnostic or not to differentiate ectopic pregnancy group from induced abortion and missed-spontaneous abortion groups. Youden Index was used to find out the best cut-off point for progesterone and also the specificity, sensitivity, positive and negative predictive value of this point was calculated. $p<0.05$ value for all results was considered to be statistically significant.

Results

The median maternal ages were 32 (20-42) years, 28 (18-42) years, 26 (19-42) years in Group 1 (admitted for induced abortion), in Group 2 (missed-spontaneous abortion group) and in Group 3 (ectopic pregnancy group) respectively. The difference between maternal ages were not statistically significant ($p= 0.266$). The median gestational age of pregnant patients in Group 2 (59 days) was significantly higher than the ones in Group 1 (49 days, $p=0.002$) and in Group 3 (48 days, $p=0.004$). The number of gravidity and parity in un-intended pregnancy were significantly higher than in ectopic pregnancy group ($p<0.001$ and $p<0.001$) and in missed-spontaneous abortion group ($p<0.001$ and $p<0.0039$). Also the number of dilation and curettage (D&C) women had in un-intended pregnancy group was significantly higher than in ectopic pregnancy group ($p<0.005$) and missed-spontaneous abortion group ($p<0.002$). There was no statistically significant difference in the previous

abortion histories (p=0.176) and in the sexually active years between three groups (p=0.058) (Table 1).

The median serum progesterone value was 19 ng/ml in unintended pregnancy group, 5 ng/ml in abortion group and 4.5 ng/ml in ectopic pregnancy group (Figure 1). The progesterone level in the unintended normal pregnancy group was statistically significantly higher than both abortion and ectopic pregnancy group (p<0.001). The difference in serum progesterone levels between ectopic pregnancy and abortion group was not statistically significant.

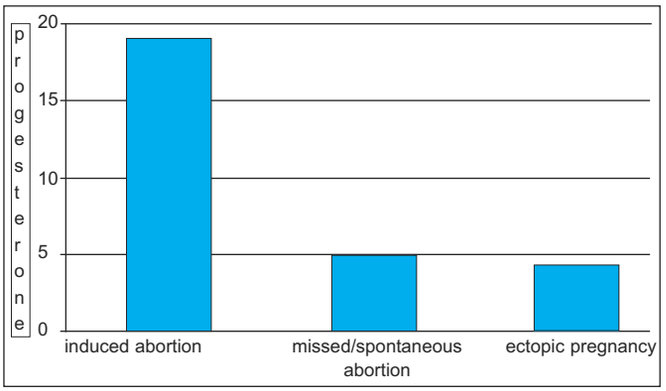

Figure 1: Progesterone serum values in groups, values are median

Progesterone was detected to be statistically significant for differential diagnosis of normal and abnormal pregnancy (p<0.001). The area under curve was 0.911 with 95% CI (confidence interval). The best cut off point was 14 ng/ml with 94.1% sensitivity, 81.8% specificity, 92.3% positive predictive and 85.7% negative predictive value (Figure 2).

The median serum β-hCG values were 44334 mIU/ml

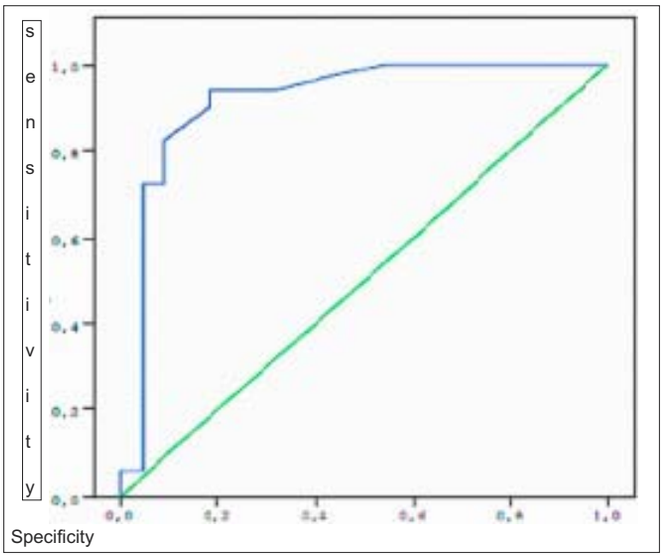

Figure 2: ROC curve for serum progesterone values

(8070-139703), 4500 mIU/ml (410-83156) and 1448 mIU/ml (221-8570) in Group 1, Group 2 and Group 3 respectively. When the three groups were compared the serum β-hCG values in unintended normal pregnancy were statistically significantly higher than the values in other groups. Also the serum β-hCG values in abortion group were higher when compared the values in ectopic pregnancy group (Table 2).

Table 1: The characteristic properties of the women in groups, values are median

Groups	Un-intended pregnancy (Group 1)	Missed-spontaneous abortion (Group 2)	Ectopic Pregnancy (Group 3)
N	22	23	28
Maternal age	32.3±6.1 (20-42)	28.8±8.2 (18-42)	30.6±6.9 (19-42)
Gestational age	49±8.5 (40-69)	59±14 (35-84)	48±9 (34-66)
Gravida	±2 (2-8)	3±1 (1-5)	3±1 (1-5)
Parity	2±1 (1-5)	1±1 (0-3)	1±1 (0-3)
D&C	1±1 (0-3)	0.1±0.2 (0-1)	0.1±0.3 (0-1)
Sexually active time(years)	6±4 (1-15)	7±4.5 (1-22	8±4 (3-18)

Table 2: Serum β-hCG, progesterone and creatine kinase values in groups

	Unwanted pregnancy group	Missed-spontaneous abortion group	Ectopic pregnancy group	Pa
B-hCG	44334 (807 -139703)	4500 (410-83156)b	1448 (221 - 8570)b,c	<0.001
Progesterone	19 (14 -41)	5 (0.7 - 19)b	4.5 (0.6 - 13)b	<0.001
Creatine Kinase	69 (40 - 132)	56 (32.2 - 312)	90 (24.9 - 352)	0.083

a: Kruskal Wallis test
b: when compared with unwanted pregnancy group, (p<0.001).
c: when compared with missed-spontaneous group, (p=0.009).

The median serum creatine kinase values in Group 1, Group 2 and Group 3 were 69 IU/l (40-132), 56 IU/l (32.2-312) and 90 IU/l (24.9-352) respectively and the difference between the three groups was not statistically significant (p=0.083**)** (Table 2).

Discussion

Since the morbidity and mortality due to ectopic pregnancy and its complications are high, early diagnosis is very important. Despite the advances in management modalities, the clinicians experience obstacles in early diagnosis and approximately 40-50% of the cases can be misdiagnosed. Various enzymes and hormones have been studied to diagnose ectopic pregnancy earlier. Here in, we studied the role of serum β-hCG, progesterone and creatine kinase levels in the diagnosis of ectopic pregnancy.

The human chorionic gonadotropin is important and the most useful serum biomarker for the diagnosis of ectopic pregnancy. The synthesis of the hormone is related with the trophoblastic tissue amount and the rapid increase in the serum values of β-hCG in 3-9 the weeks of pregnancy is due to the rapid growth of immature trophoblastic tissue.[12] Currently, β-hCG is usually used with TVS for the assistance of diagnosis of EP. In an intrauterine pregnancy, a single value of β-hCG is useful generally when the gestational sac is visible on the ultrasonography (the discriminatory level), but below this level serial β-hCG values are needed to make differential diagnosis of viable intrauterine pregnancy from EP or non-viable intrauterine pregnancy.

An expectant management based on β-hCG and progesterone serum values firstly evaluated in 1995 by Hahlin et al. [13] and then in 1999 Banerjee et al.[14] and Facey et al.[15] have suggested the same approach as safe and successful. However, even in following-up serial serum β-hCG values the expected rise in serum values in 48 hours in a viable intrauterine pregnancy varies from 35% to 66% [16] and also observing serial values takes time and increases the risk of tubal rupture which is life threatening. In a study of Bignardi T. et al. the viability of a pregnancy which cannot be localized on ultrasonography was studied by comparing the hCG ratio (hCG 48 h/hCG 0 h) and initial serum progesterone level. They suggested that hCG ratio can be preferable to single progesterone level in predicting the viability of pregnancy with unknown localization.[17] Similarly in our study, the serum β-hCG values were significantly higher in normal pregnancies and helpful to differentiate normal pregnancies from abnormal (abortion or ectopic) pregnancies. Also the values were higher in missed-spontaneous abortion group from ectopic pregnancy group.

In our study, we found that serum progesterone value was well in differentiating normal pregnancy from abnormal ones. When we took 14 ng/ml as the best cut-off value of progesterone, with 94.1% sensitivity and 81.8% specificity this serum value can make the differential diagnosis of normal pregnancies. But the serum progesterone values were not discriminative between ectopic pregnancies and pregnancies that resulted with abortion. Our results were similar with the study of McCord et al. in which the serum progesterone values of a total 3674 patients with intrauterine pregnancy, spontaneous abortion and ectopic pregnancy were compared. They suggested that 17.5 ng/ml cut-off point of serum progesterone level was effective to differentiate normal pregnancies from abnormal ones.[18]

In a study of Dart R et al. studied 160 patients admitted to emergency department with serum β-hCG values below 3000 mIU/ml and unknown localization on ultrasonography. They suggested that the serum progesterone value below 5 ng/ml pointed out abnormal pregnancy with 97% specificity and 84% sensitivity and ectopic pregnancy with 88% sensitivity and 40% specificity.[19] Buckley R et al. suggested that >22 ng/ml value of serum progesterone was able to exclude ectopic pregnancies.[20]

Stewart et al suggested that one serum progesterone value was not enough to differentiate ectopic pregnancy from intrauterine pregnancy, on the other hand could differentiate normal from abnormal pregnancy (abnormal intrauterine and ectopic pregnancy). In their study the cut-off serum progesterone level was taken as 8 ng/ml.[21] Similarly in our study we found that only one serum progesterone value was able to differentiate normal pregnancy from abnormal but not able to make the differential diagnosis between ectopic and abnormal intrauterine pregnancy. Low level of synthesis of β-hCG in ectopic pregnancy can explain this situation since β-hCG is the main source of progesterone production in early pregnancy. In ectopic pregnancy trophoblasts proliferate slowly so that the production of β-hCG is less.[22]

Payne et al. in their study with rat uterus and placenta suggested the important role of creatine kinase in the prognosis of pregnancy.[23] Since there is no submucosal layer in the fallopian tubes, the ectopic pregnancy localized on the tubes pass to muscular layer after invading tubal mucosa. The trophoblastic invasion in muscular layer destroys the muscular layer and vessels there. Laive et al. suggested that after cell destroys, creatine kinase arise and pass to maternal circulation and the level increase in maternal serum.[24] In their study the serum level 45U/l of creatine kinase was much higher than normal pregnancy and abortion group and they concluded that above this level the risk of ectopic pregnancy increased. In a similar study of Saha et al. in 1999 20 ectopic and 20 normal pregnant were studied and serum creatine kinase levels of patients with

ectopic pregnancy were found significantly higher than the normal pregnant.[25] Also in 2002 Develioğlu et al studied 32 ectopic and 21 normal intrauterine pregnancies. They found that the serum CK levels were significantly higher in isthmic pregnancies than ampullar and normal intrauterine pregnancies and also higher in ruptured ectopic pregnancies than unruptured ectopic pregnancies.

When the cut-off serum value of CK was taken as 120 IU/l it was able to differentiate ruptured ectopic pregnancies with 65% sensitivity and 87% specificity; however the primary use of serum CK level in the diagnosis of ectopic pregnancy was not thought to be helpful.[26] In a study of Soundrovally et al. in 2007 the cut-off serum value of CK of 145 IU/l was suggested to differentiate ruptured pregnancy from unruptured one with 95.7% sensitivity and 98% specificity. Also the serum value of CK 68 IU/l CK was stated to be 100% sensitive and 82.5% specific for ectopic pregnancy.[27]

On the other hand, in 2001 Robert et al. compared the serum CK levels in a total 378 and of 61 ectopic patients who admitted to emergency department with pelvic pain and vaginal bleeding in the first trimester. They concluded that serum CK level was not helpful in differential diagnosis of ectopic pregnancy.[28] In 2005 Condous et al investigated the serum CK levels of 28 ectopic, 116 intrauterine normal and 153 missed abortion patients; the difference between CK median values of ectopic and normal pregnant was not significant. So they suggested the serum CK levels were not helpful in ectopic pregnancy diagnosis.[29]

In our study the median serum CK level in ectopic pregnancy group was higher than the levels of normal pregnancy and abortion group but the difference was not statistically significant.

In conclusion, serum biomarkers for early diagnosis of ectopic pregnancies are under investigation. Up to date new biomarkers have been used for this purpose. However, till these new biomarkers will be verified by randomized controlled trials conventional biomarkers, progesterone and beta-hCG are the best choice especially if combined with transvaginal ultrasonography in the differential diagnosis of normal and abnormal pregnancies.

Ektopik Gebeliğin Erken Tanısında Beta-hCG Progesteron ve Kreatin Kinazın Rolü

AMAÇ: Ektopik gebelik (EG) hayatı tehdit eden birinci trimester kanamalarının önemli bir sebebi olduğu için erken tanısı önemlidir. Bu çalışmamızda kreatin kinaz, progesteron ve beta-hCG'nin EG erken tanısında önemini araştırmak istedik.

GEREÇ VE YÖNTEM: Temmuz-Kasım 2008 tarihlerinde Ankara Eğitim Araştırma Hastanesi'ne başvuran 73 hasta çalışmaya alındı. Hastalar üç gruba ayrıldı. Grup 1'e (n=22) aile planlaması polikliniğine erken gebelik terminasyonu için başvuran hastalar, Grup 2'ye (n=23) spontan veya missed abort tanısı alan hastalar ve Grup 3'e (n=28) ektopik gebelik tanısı alan hastalar dahil edildi. Hastalara herhangi bir girişim yapılmadan önce β- hCG, progesteron ve kreatin kinaz ölçümleri için kan alındı. Verilerin analizi SPSS for Windows 11.5 paket programında yapıldı.

BULGULAR: Normal gebelik grubunda progesteron düzeyinin diğer iki gruba göre istatistiksel olarak anlamlı derecede yüksek olduğu saptandı (p<0,001). Ektopik gebelik ve spontan abortus grupları arasında ise bu açıdan anlamlı bir fark gözlenmedi. Progesterona ait en iyi kesim noktası %94,1 seçicilik ve %81,8 hassasiyet ile 14ng/ml olarak hesaplandı. Serum β-hCG düzeyi normal gebelik grubunda anormal gebeliklere göre (missed, spontan abortus ve ektopik gebelik) istatistiksel olarak anlamlı düzeyde yüksek bulundu. Kreatin kinaz değerleri bakımından her üç grup arasında istatistiksel anlamlı fark bulunamadı (p=0,083).

SONUÇ: Beta-hCG ve progesteron anormal gebeliği erken teşhis etmede faydalıdır fakat ektopik ve anormal intrauterin gebelikleri ayırt edemeyebilir. Kreatin kinaz EG ve normal gebelikleri ayırt etmede faydalı değildir.

Anahtar Kelimeler: Ektopik gebelik, Beta-hCG, Progesteron, Kreatin kinaz

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