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Study of Differentiated Beta-Human Chorionic Gonadotropin Serum (BhCG), Progesterone and CA-125 in Patients with Tubal Ectopic Pregnancy

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ABSTRACT

Ectopic pregnancy (EP) is 6-10% of all pregnancy related deaths. The incidence of EP is 1-2% in the developed countries. In the present study we evaluated the serum BhCG, progesterone and CA-125 level in the efficacy of methotrexate for treatment of ectopic tubal pregnancy. Over a period of two years, 61 patients with the diagnosis of ectopic pregnancy included in study. 30 cases were in methotrexate (MTX) treatment group and 31 cases in surgical treatment group. Sera of samples were assayed for BhCG, progesterone and CA-125. Analyses were performed using SPSS version 16 computer software. T-test and chi square, Roc analysis was used for Sensitivity and specifity. Mean of baseline BhCG level at initial presentation was 439±363 in MTX group and 1027±722 in surgical treatment group; These levels in two groups were significantly different (p=0.001). Mean of initial serum progesterone level was significantly higher in surgical treatment group than medical treatment group (p<0.006). In addition, no statistically difference was observed in CA-125 between two groups (p<0.671). Finding of this study showed that pretreatment serum BhCG and progesterone level had meaningful relation with the efficacy of medical treatment of ectopic pregnancy; Also in this study CA-125 was not a predictor of MTX treatment.

Key words: Ectopic pregnancy, Medical treatment, BhCG, Progesterone, CA-125

1. INTRODUCTION

Implantation of a fertilized ovum outside the uterine cavity is known as ectopic pregnancy (EP) (1-3). In the United States between 1980 and 2007 years, 876 deaths were attributed to EP. The EP maternal mortality ratio declined by 57 percent between the years of 1980 to 1984 and 2003 to 2007, from 1.15 to 0.50 deaths per 100,000 live births (4). EP leads to 6-10% of all pregnancy related deaths (5). Global studies estimated that the prevalence of EP is 1-2% (6). EP is an important cause of maternal mortality in addition to infertility, till date. EP still considered for 4-10% of pregnancy- related deaths along with the complications associated with the increased demand of blood transfusion (7). Unruptured EP can be diagnosed rapidly and accurately with the use of transvaginal ultrasonography in conjunction with a quantitative serum human chorionic gonadotropin (hCG) test (8). Systematic reviews demonstrate that ultrasound scans performed in the emergency department have sensitivity (90%) and specificity (98%) in the detection of an intrauterine pregnancy (9). Early diagnosis of EP is possible by specific assays of B- subunit of hCG and high resolution ultrasonography with vaginal probes (10). Progesterone has also been studied extensively as an adjunct for transvaginal ultrasound and hCG levels. Early in pregnancy, progesterone is secreted by the corpus Luteum and is a critical hormone for the establishment of normal pregnancy (11). Only 0.3% of patients with a viable intrauterine pregnancy had serum progesterone value less than 5 ng/ml and 2.6% of patients with a serum progesterone level higher than 20ng/ml had an EP (12).

Markers of inflammation and peritoneal irritation such as CA-125 have also been investigated for discrimination of EP (13-16). The CA-125 tumor marker is a cell- surface antigen derived from the surface coelomic epithelium including the mucosa of the entire female genital tract and the germinal epithelium of the ovaries (17). The fetal chorion, amniotic fluid, and maternal deciduas also contain significant amounts of CA-125 protein (18). EP is a unique situation in which maternal extra-uterine compartments that are exposed to fetal tissues (19). Conservative management of unruptured ectopic pregnancy using single dose MTX with the aim of conserving the tube was first described by Stovall et al (20). There are some cases which resolve with single dose of MTX but there are some who require an additional dose. There are some cases in which tubal rupture occurs after MTX treatment that risk of this ranging is 7% to 14% (21-28). In the present study we evaluated the serum BhCG, progesterone and CA-125 level in the efficacy of methotrexate for treatment of ectopic tubal pregnancy.

2. MATERIALS AND METHODS

This study was conducted in the department of obstetrics and gynecology in Kermanshah University Medical sciences (years: 2012-2013). The 61 patients with the definite diagnosis of ectopic pregnancy included the study that 30 cases considered in MTX treatment group and 31 cases considered in surgical treatment group. Diagnosis was confirmed by sensitive BhCG assay and transvaginal ultrasound. Inclusion criteria for conservative management was hemodynamic stability, ectopic mass size less than 4 centimeter, serum BhCG level less than 10000 mIU/ml, absence of free fluid in abdominal cavity. Those with ruptured EP, visualization of fetal heart in ectopic mass, hepatic, kidney and platelet dysfunction, were excluded from the study. Single intramuscular injection of MTX (1 mg/kg body weight) was given to eligible patients. A second dose was given to those cases in which decrease in BhCG between days 4 and 7 was less than 15 % (29). Patients were followed weekly until serum BhCG level reached less than 10 mIU/ml. In those with sign and symptom with hemoperitoneum and those did not respond to second dose of MTX all laparotomy requirements done. At the initial visit pretreatment sera of samples were assayed for BhCG, progesterone and CA-125. University Research Committee approved this study (research committee code: 92104). CA-125 was measured by chemiluminescence (cl) method with the device liason Manufacturing Co. Diasorn Italy. Progesterone was assayed by ELIFA (Enzyme Linked Fluorescent Assay) with the device vidas Manufacturing Co; Biomerieux France and BhCG was measured by IRMA (Immunoradhometric assay) method with the device Gamma counter Co. Riakey korea. Analysis of achieved data were performed using spss version 16 computer software; Roc analysis was used for Sensitivity and specifity. A p-value less than 0.05 ($p_{value} < 0.05$) was considered as statistically significant.

3. RESULTS AND DISCUSSION

The characteristics of 61 women with EP who received medical and surgical management are presented in Table 1.

Table 1. Baseline characteristics of population study

Types	Medical group (Mean±SD) (n=30)	Surgical group (Mean±SD) (n=31)	p.value
Maternal age(years)	5.9±29.3	7.1±26.6	0.118
Gestational age(week)	1.4±6.6	0.7±6.1	0.148
Gravidity	1.4±2.2	0.8±1.7	0.089

No significant difference was observed in terms of maternal age, gestational age and gravidity between patients with medical and surgical treatment group. Mean of baseline BhCG (mIU/ml) level at initial presentation was 439±363 in MTX group and 1027±722 in surgical treatment group; these levels in two groups were significantly different (p=0.001). Mean of initial seem progesterone level was significantly higher in surgical treatment group than medical treatment group (p<0.006) table 2. Regarding CA-125 no statistically difference was observed between two groups (p<0.671) Table 2.

Table 2. Mean of serum biomarkers and ectopic mass size in population study

Types	MTX treatment (Mean±SD) group(n=30)	Surgical treatment (Mean±SD) group(n=31)	P.value
BhCG (mIU/ml)	363±439	772±1027	0.001
Progesterone (ng/ml)	6.2±8	6.4±14.7	0.006
CA-125 u/ml)(	19.3±25.9	9.3±27.5	0.671
size Ectopic mass mm^2)(	200±353	154±387	0.502

Mean of ectopic mass size (mm^2) was 353±200 and 387±154 in MTX treatment and surgical treatment group respectively; the found difference was not significant. Based on Roc Test 83.3% Sensitivity and 66.4% specifity was found for serum hCG level of 364 (mIU/ml). In the serum HCG, level of Sensitivity (947) reduced to 50% but specifity increased to 89%. Regarding progesterone sensitivity was 90% and specifity was 80.8% at serum progesterone level of 7.9 ng/ ml, CA-125 at serum level of 18.8 u/ml Sensitivity and specifity was 86.7% and 50% respectively. According to ectopic mass size at 356 mm^2 level, Sensitivity and specifity was 53.3% and 53.8% respectively. Area under the ROC curve shows the diagnostic power of biomarkers in the efficacy of treatment with MTX. (Figure 1, Figure 2, Figure 3 and Figure 4).

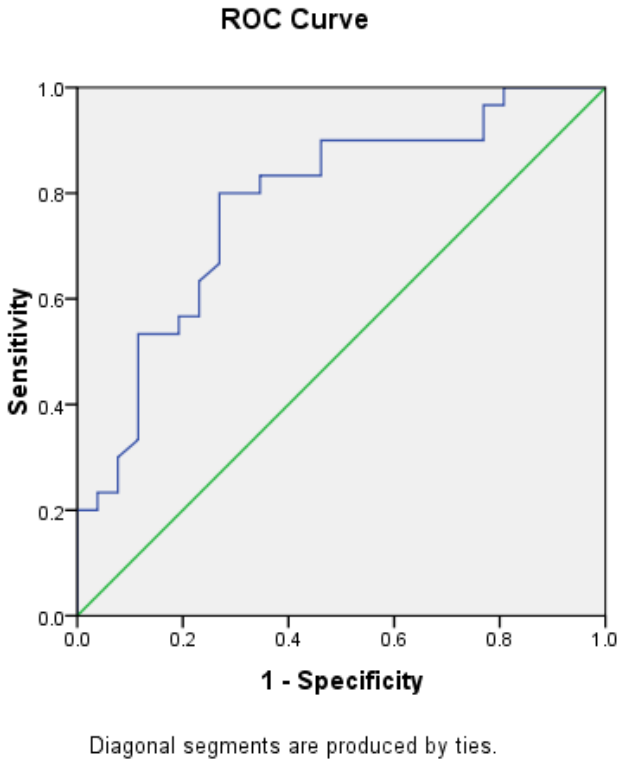

Figure 1. ROC curve sensitivity and specificity for BhCG

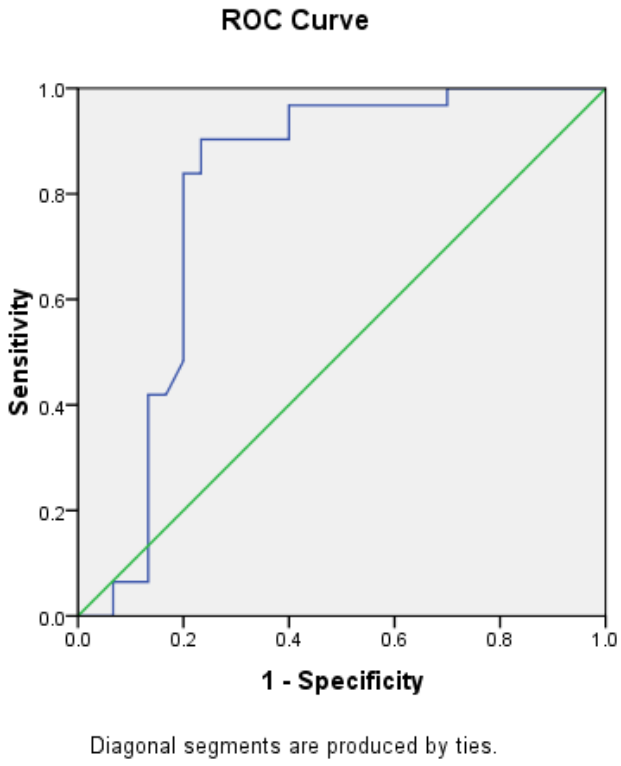

Figure 2. ROC curve sensitivity and specificity for progesterone

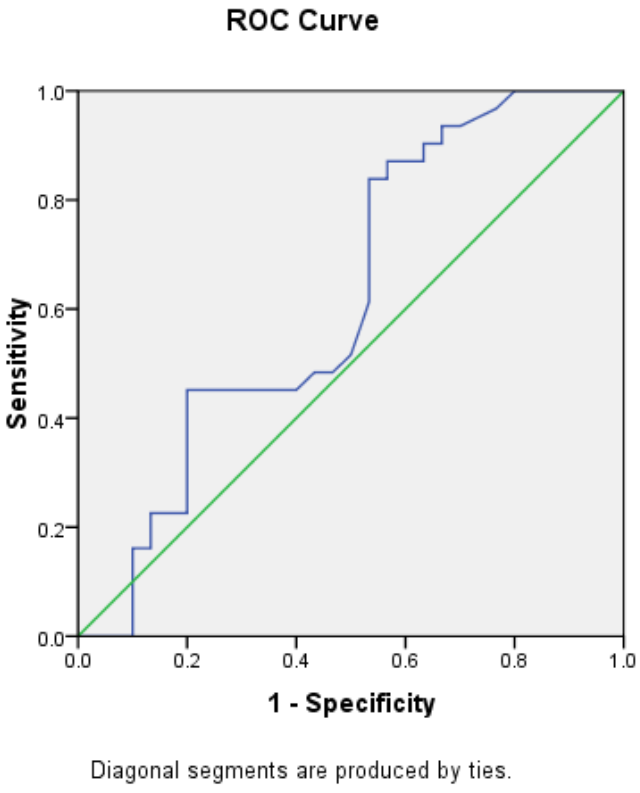

Figure 3. ROC curve sensitivity and specificity for CA-125

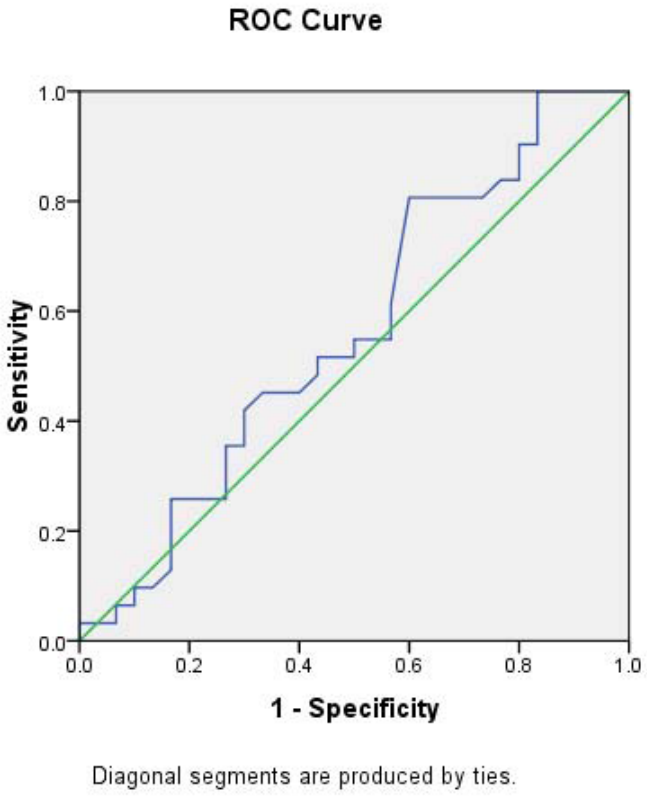

Figure 4. ROC curve sensitivity and specificity for ectopic Mass size

In the present study the CA-125 in two groups of treatment was not significantly different 27.5±9.3 in surgical versus 25.9±19.3 in medical treatment group. This may be explained by the impaired interaction between the fetal trophoblast and tubal mucosa (30). It was believed that destruction of fetal tissues and / or oviduct mucosa would yield different serum CA-125 values in patients with EPs compared with patients with intrauterine pregnancies (31). The results of this study are similar with the study of Meenu Meta who found low level of CA-125 in patients with EP. Systemic use of MTX has been proven to be successful in the medical management of unruptured ectopic pregnancies. According to a study conducted by Lipscomb et al (32) in Memphis (n=350), initial level of BhCG was the best prognostic factor in prediction the success of treatment. They found a 94% success rate when initial BhCG level was <10000 mIU/ml and 75% success rate when it was above 10000 mIU/ml. They concluded that an initial BhCG level above 10000 mIU/ml was a risk factor for MTX treatment failure. Gyum Joon Cho et al (33) On 126 korean woman concluded that pretreatment Hcg level was the only predictor of treatment success with multiple dose of MTX. In a previous research by our team, we found a success rate of 64% on 139 patients with single dose of MTX. The mean initial BhCG level at the time of treatment was 523.72±674.13 mIU/ml (29). Our study showed that biomarkers of BhCG and progesterone have high predictive value in the efficiency of MTX treatment. In this study we found that BhCG level at 364 mUL/ml had sensitivity (83.3%) and specifity (66.4%) in the efficiency of MTX treatment of EP. In another study by Stika et al (34), 50 patients with EP were treated with a single dose of MTX and it was concluded that cases with initial serum BhCG level >5000 mIU/ml had a greater probability of requiring either multiple dose of MTX or surgical intervention. It is evident that different studies have suggested different cut- offs for BhCG level that may be due to varying inclusion and exclusion criteria, varying sample size, varying number of doses of MTX used and different study populations. Ectopic mass size has also been found to be an important variable in some studies. In our study the difference in ectopic mass size between two groups of treatment was not significant. Our teaching hospital is a referral center and almost all patients with EP and hemodynamic stability are referred for medical treatment and we had no limitation in performing project.

4. CONCLUSION

Finding of this study showed that pretreatment serum BhCG and progesterone level had meaningful relation with the efficacy of medical treatment of ectopic pregnancy. In this study, CA-125 was not a predictor for MTX treatment.

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AUTHORS CONTRIBUTION

This work was carried out in collaboration among all authors.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

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