Original article

Diagnostic accuracy of serum activin A in detection of ectopic pregnancy

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Background: Ectopic pregnancy (EP) still remains a main cause of maternal mortalities. This study is designed to evaluate the accuracy of serum Activin A in detection of ectopic pregnancy. **Methods**: This prospective observational study was conducted from 2009 to 2010 at two main referral university hospitals, Isfahan University of Medical Sciences, Isfahan, Iran. Two hundred subjects who were under 10 week's pregnancy with clinical presentations of abdominal pain and vaginal bleeding were enrolled. After sampling serum Activin A, patients underwent ultrasonography, titer of B-HCG and surgery (if indicated) and were divided into two groups: EP (n = 100) and intrauterine pregnancy (IUP) (n = 100). The mean of Activin A was compared between groups and by ROC curve, the optimal cut off with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were determined. **Results**: The mean age of women with IUP was 25.4 ± 4.3 years (15-40 years) compared with 25.9 ± 4.1 years in women in EP group (P = 0.448). Statistical difference was not found between EP versus IUP groups in gestational age (6.32 ± 1.03 vs. 6.85 ± 1.82 weeks, P = 0.124). The mean of serum Activin A in EP group was 0.264 ± 0.0703 ng/ml versus 0.949 ± 0.5283 ng/ml in IUP group (P < 0.05). According to ROC curve (area under the curve = 0.981, P < 0.05, confidence interval: 0.961-1.000), the optimal cut off was estimated as 0.504 ng/ml with sensitivity of 97% and specificity of 93.5%. **Conclusion**: This study indicated that the mean of serum Activin A is lower in EP compared with IUP. The serum Activin A has a fair accuracy in detecting EP.

Key words: Activin A, ectopic pregnancy, sensitivity, specificity

INTRODUCTION

Ectopic pregnancy (EP) still remains one of the mortality reasons among pregnant women. Insufficient evaluation and delayed diagnosis are the most common causes for the mortalities due to EP.[1] Therefore, many studies were designed to find the accurate method in detection of EP. Currently, transvaginal ultra sonography is an acceptable diagnostic method in women who are suspected to have EP.[1,2] Indeed, with transvaginal ultra sonography, intra uterine pregnancy can be defined even in gestational age of 30 days.[3] However, this diagnostic method is unable to detect the EP in 8-31% of cases.[1] In these cases, surgery or assessing biochemistry markers such as human choriogonadotropin hormones and progesterone can be useful.[1,4,5] The disadvantages such as inaccuracy and nonreliability of the defined methods led the scientists to find a novel accurate diagnostic way for detecting EP.

Activin A, a dimeric glycoprotein, is a subgroup of TGF-B with similar structure and different function. This protein is a growth factor which represents the cellular proliferation and development.[6] During pregnancy, Activin A is secreted from placenta and increases until delivery.[6] Previous studies demonstrated that serum level of Activin A decreases in dead trophoblasts.[7,8] Therefore, Florio and colleagues reported that serum level of Activin A is lower in EP compared with IUPs, which may be because of incomplete trophoblast invasion.[9] However, there are only few studies on the evaluation of serum Activin A in detecting EPs and our knowledge concerning the accuracy of this diagnostic test is limited. Therefore, this study is designed to evaluate serum Activin A in detection of EP.

METHODS

This prospective observational study was conducted from 2009 to 2010 at a referral university hospital (Al-Zahra), Isfahan University of Medical Sciences, Isfahan, Iran. Patients with positive B-HCG and clinical features of vaginal bleeding and abdominal pain who were of <10 weeks gestational age were enrolled in the study. Exclusion criteria were using exogenous progesterone, abortion, Hydatidiform Mole and patients who underwent treatment for EP. . The study was approved by the Ethics committee of Isfahan University of medical sciences, and each patient gave informed consent prior to the study after full explanation of the study aims and protocol, in accordance with the ethical

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standards of 1964 declaration of Helsinki as revised in 2000.

After registering demographic data and medical history such as maternal and gestational age, history of EP and abortion, the basic level of B-HCG and serum Activin A were assessed and the women underwent transvaginal ultra sonography (TVS) with 4.5-7 mHz probe by expert radiologists. The diagnosis of IUP was established with finding of normal sac of pregnancy in uterus along with normal tubes and adnexa. If EP is suspected, patients were followed in vital signs, serum level of B-HCG and TVS each 48 h. Patients who had unstable vital signs, clinical features of intra-abdominal bleeding or abdominal mass size of >3.5-4 cm underwent emergency surgery (laparatomy or laparoscopy). With regard to TVS findings, clinical evaluation and surgical results, the women were divided into two groups: EP (n = 100) and IUP (n = 100).

The comparison of serum level of Active A between EP and IUP was the primary outcome and determination of cut off, with the help of ROC curve, and its sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were the secondary outcomes.

After collecting the data, the results were analyzed with SPSS (version 16) software with the help of independent t-test, Chi-square and ROC curve. P value lower than 0.05 was defined as statistical difference.

RESULTS

The mean of maternal age was 25.4 ± 4.3 years (15-40 years) in EP group and 25.9 ± 4.1 years (16-41 years) in intrauterine pregnancy group. According to t-test, there was no statistical difference between groups (P = 0.448). The mean of gestational age was 6.32 ± 1.03 weeks in EP group compared with 6.85 ± 1.82 weeks in IUP group (P = 0.124). The parity of pregnancy was not statistically different between groups (1.27 ± 0.59 vs. 1.95 ± 0.38, P = 0.322). Eleven (11%) women in EP group and 10 (10%) women in intrauterine group had history of one abortion (P = 0.884). The history of two abortions was found in one person in each group (P = 0.822).

The mean of serum Activin A was 0.264 ± 0.0703 ng/ml versus 0.949 ± 0.5283 ng/ml in EP and IUP groups. According to independent t-test analysis, there was statistical difference between two groups (P < 0.05).

With the help of ROC curve, the serum level of Activin A had a fair accuracy in detecting EP (area under the curve = 0.981, P < 0.05, confidence interval: 0.961-1.000). Diagram 1 shows ROC curve in determining EP.

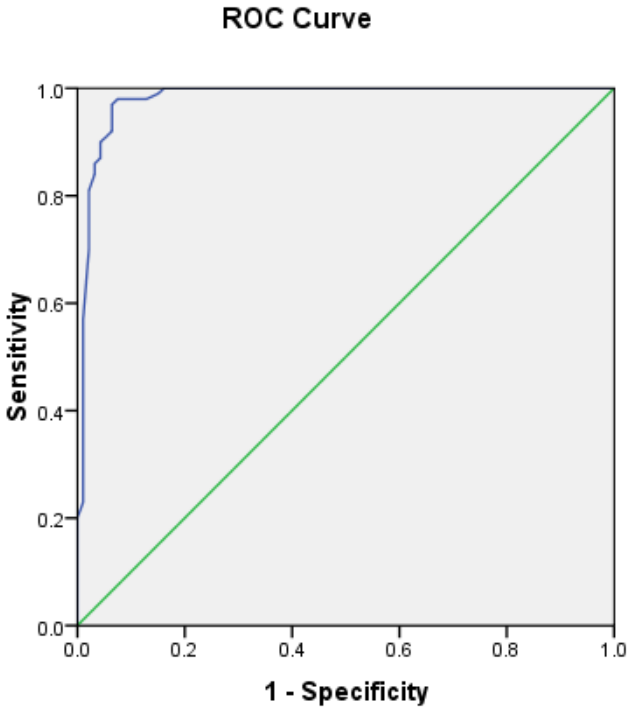

Diagram 1. ROC curve of serum activin A testing in determining EP

With the help of ROC curve, the optimal cut off was estimated about 0.504 ng/ml. In this cut off, the sensitivity and specificity were 97 and 93.5%. If serum Activin A concentrations were low (i.e. below the thresholds defined by the ROC curve analysis), its positive and negative predictive value for EP were as high as 94.1 and 96.6%.

DISCUSSION

This study showed that the mean of Activin A was lower in EP compared with IUP. The serum level of Activin A had a fair accuracy in detecting EP. The optimal cut off was 0.504/μl. In this cut off, the sensitivity of 97%, specificity of 93.5%, PPV of 94.1% and NPV of 96.6% were assessed.

Knowledge of lower serum level of Activin A in EP versus IUP is a novel finding which may be due to incomplete implantation and deficient trophoblast invasion. Indeed, normal increasing of serum level occurs during pregnancy. Therefore, any variety in serum level of Activin A may represent serious problems.[10] Nowadays, decreasing serum level of Activin A was defined in problems such as abortion,[8] preeclampsia,[11] intrauterine growth retardation[12] and placenta abruption.[13] This evidence suggests that a reduction of Activin A secretion in EP may signal the difficulty of the trophoblast to correctly implant. Indeed, *in vitro* data on the role of Activin A in facilitating endometrial decidualization[14,15] and the fact that decidualization is a requisite for successful implantation. This collectively leads us to hypothesize that an impairment of Activin A synthesis and release may take place in the placenta, causing the lack of a well-vascularized and appropriately constructed endometrium and, therefore, trophoblast implantation outside the uterus.

This study showed the serum Activin A was statistically lower in EPs versus IUP. This finding supports the previous studies.[11] In contrast, Kirk and colleagues [16] assessed Activin A in 140 women and found no statistical difference in Activin A between EPs and intrauterine pregnancies. This difference may be due to the difference in sample size and inclusion criteria.

Florio and colleagues[11] in 536 women with unknown pregnancy location assessed the serum level of Activin A in EPs and showed the optimal cut off was 0.37 ng/ml. The sensitivity and specificity of 100 and 99.6% were found in their study. In this study, the sensitivity and specificity were 97 and 93.5%. This difference may be because of difference in sample size.

So far, limited studies were designed to evaluate the serum level of Activin A in detecting EPs and we recommend further study for evaluation of this test.

CONCLUSION

This study indicated that the serum level of Activin A is statistically lower in EP than IUP. This test has a fair accuracy in detecting EPs. Further studies are warranted.

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