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Serum CA-125 in Normal First Trimester of Pregnancy and Ectopic Pregnancy

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ABSTRACT

Objectives: To compare the mean serum CA-125 level between normal first trimester pregnancy and ectopic pregnancy, and to determine the cut point of CA-125 level for diagnostic aim.

Methods: This cross-sectional study was conducted at Department of Obstetrics and Gynecology, Faculty of Medicine, Vajira hospital, Navamindradhiraj University between December 2012 and September 2013. Two compared groups were invited from 2 resources. The first group was normal intrauterine pregnant women who came to antenatal care unit. Another group was women with diagnosed ectopic pregnancy and further pathologically confirmed. Blood was drawn from each woman for standard antenatal/preoperative laboratory investigations along with serum CA-125. Levels of CA-125 between both groups were compared. The prediction of ectopic pregnancy was assessed by receiver-operating characteristic (ROC) curve.

Result: There were 30 normal pregnancies and 30 ectopic pregnancies in this study. No statistically significant difference was found in terms of age, parity, and gestational age between normal and ectopic pregnancy group. The mean serum CA-125 level in ectopic pregnancy group (24 ± 10 IU/ml) was lower than normal pregnancy group (48 ± 36 IU/ml) which statistically significant difference (P value 0.02). When serum CA-125 level of 30 IU/ml was used as a cutoff value for diagnosis of ectopic pregnancy; sensitivity 73.3% and specificity 73.3%.

Conclusion: The measurement of serum CA-125 levels may be useful in discriminating ectopic from normal intrauterine pregnancy.

Keyword: normal pregnancy, ectopic pregnancy, first trimester, CA-125

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Introduction

Ectopic pregnancy is one of abnormal gestation that implantation occurred outside endometrial uterine cavity, which tubal pregnancy is the most common site[1,2]. Ruptured tubal gestation is the serious outcome of ectopic pregnancy that may be leading to massive intra-abdominal hemorrhage, hypovolemic shock and maternal death if delay in diagnosis and treatment.

Classic triad of symptoms of ectopic pregnancy is lower abdominal pain, missed period, and vaginal bleeding[5]. Unfortunately, there are no physical findings unique to ectopic pregnancy; similar symptoms are observed commonly in women with other pregnancy-related problems such as threaten abortion. There are numerous investigations has been used to discriminate between intra-uterine gestation and ectopic gestation[6]. However, in some cases are inconclusive and may be lead to more invasive testing, like diagnostic laparoscopy or dilatation and curettage[5].

Cancer antigen 125 (CA-125) is a glycoprotein antigen that expressed in more than 80% of epithelial ovarian cancer patients[7-9]. There are some limitations of using CA-125 in reproductive age women because it also increases with other pelvic conditions such as endometriosis, leiomyoma, pelvic inflammatory disease and the first trimester of pregnancy[9,10]. Numerous studies have been attempted to demonstrate as a marker for diagnoses ectopic pregnancy with the rationale that ectopic pregnancy had lower CA-125 level than normal pregnancy because placenta cannot growth as well as normal[11,12]. In addition, the results from these studies were inconclusive in view of diagnostic purpose and predicting value of rupture[8,12]. Therefore the primary objective of this study is to compare mean serum CA-125 level between normal pregnancy and ectopic pregnancy, and to determine the cut point of CA-125 level for diagnostic aim.

Materials and methods

A cross-sectional study was conducted at Department of Obstetrics and Gynecology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University between December 2012 and September 2013. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the study protocol was approved by Vajira ethical committee.

Participants in this study were invited from 2 resources. The first group was normal intrauterine pregnant women who came to antenatal care unit. Another group was women with suspected ectopic pregnancy base on present history, physical examination, pregnancy test and sonographic findings. All normal intrauterine pregnancy were in the first trimester of gestation as calculated by the first day of last menstrual period or with corrected ultrasound in some women with uncertain date and were confirmed viable single intrauterine gestation with ultrasound. All ectopic pregnant women were confirmed diagnosis with pathological report of tissue that collected from surgical intervention either laparoscopy or laparotomy. Exclusion criteria were women who have current PID (pelvic inflammatory disease), current endometriosis, uterine fibroid, multiple gestations, non-tubal ectopic pregnancy, ectopic pregnant women who were not undergo surgical treatment, and hemodynamic instability patients.

After informed consent was obtained, each pregnant woman was interviewed for the following information: demographic data, menstrual and obstetrics history, medical and surgical history. All women underwent venipuncture and blood was drawn either at the same time of first laboratory checking for antenatal care or at the time of pre-operative laboratory checking from normal and ectopic pregnant women, respectively. The activity of CA-125 was measured by ELISA (Roche Diagnostics, Warsaw, Poland).

Assuming a two-sided alpha level of 0.01 and 90% power, we performed a power analysis base on available mean CA-125 levels and standard deviations. The mean CA-125 in normal pregnancy and in ectopic pregnancy has been found to be 154 and 33, respectively with pooled variance of 13,542. The number of needed subject in each group was 28 women.

The values of mean serum CA-125 were compared between normal intrauterine pregnancy

group and ectopic pregnancy group. Receiver Operator Characteristic (ROC) curve was created to show sensitivity against specificity of low CA-125 as diagnostic test for ectopic pregnancy. The cut-off value of significant sensitivity and specificity was determined. Subsequently, positive and negative predictive values were calculated. All analyses were performed using STATA version 10 computer software. A p-value of less than 0.05 was considered statistically significant.

Results

There were 30 normal pregnancies and 30 ectopic pregnancies in this study. The basic demographic data of both groups are presented in Table 1. No statistically significant difference was found in terms of age, parity, and gestational age between normal and ectopic pregnancy group. However, there was significant difference of body mass index between 2 groups. The most common clinical presentation of ectopic pregnant women was pelvic pain (76.7%). Only 23.3% of all ectopic pregnancies present with vaginal bleeding. Most ectopic gestations had abnormal adnexal mass (83.3%), followed by abnormal free-fluid in cul de sac (66.7%) which was detected by ultrasonography.

The mean serum CA-125 level in ectopic pregnancy group was significant lower than normal pregnancy group, as show in Table 2. The ROC curve demonstrated a significant discriminatory ability of decreased CA-125 level for the diagnosis of ectopic pregnancy, as show in Fig. 1. When serum CA-125 level of 30 IU/ml. was used as a cut-off value for diagnosis of ectopic pregnancy; sensitivity was 73.3%, specificity was 73.3%, and negative predictive value was 73.3%, while positive predictive value was 73.3% (Table 3). However, at this cut point when based on overall prevalence of ectopic pregnancy in general population that has been reported about 2%, the predictive value of negative was 99.3% and the predictive of positive was 5.3%.

Table 1. Demographic data and baseline characteristics.

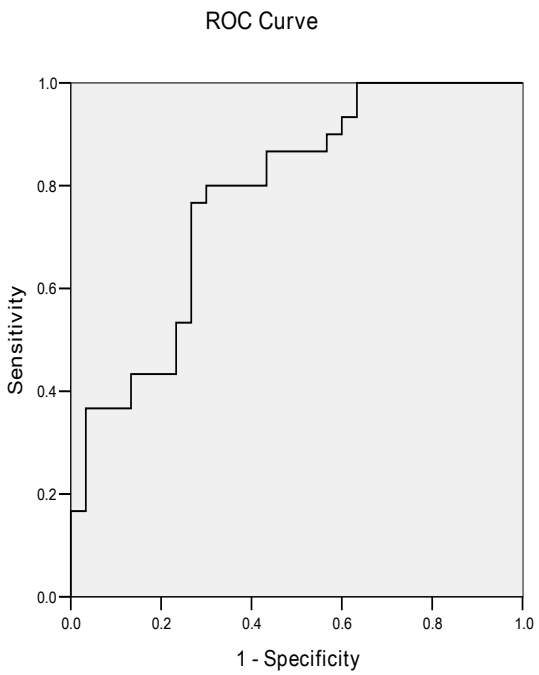
	Normal pregnancy N=30 Mean±SD or n (%)	**Ectopic pregnancy N=30 Mean±SD or n (%)**	**p***
Age (years)	27.6±5.3	24.9±5.6	0.066
Parity			0.301
- Nulliparous	16 (53.3)	12 (40)	
- Multiparous	14 (46.7)	18 (60)	
Gestational age (days)	56±10.2	53.9±8.8	0.411
BMI (kg/m^2)	20.7±3.9	23.7±3.2	0.001

Note: BMI = Body Mass Index, *using t-test in continuous data or Chi-square test in categorical data as appropriate

Table 2. Serum CA-125 level in normal and ectopic pregnancy groups.

Group	serum CA-125 (IU/ml)				p
	Mean	SD	95% Confident Interval		
Normal pregnancy	48.4	36.0	34.9	61.8	0.002*
Ectopic pregnancy	24.0	10.0	20.2	27.8	
- Unruptured ectopic pregnancy	25.6	12.4	17.8	33.5	0.476#
- Ruptured ectopic pregnancy	22.9	8.4	18.7	27.1	

Note: * comparing mean serum CA-125 between normal and ectopic pregnancy by Wilcoxon Rank Sum test, # comparing mean serum CA-125 between unruptured and ruptured ectopic pregnancy by Wilcoxon Rank Sum test



Note: AUC=0.779, SEM=0.059, 95%CI=0.663- 0.895

Fig. 1. Receiver Operator Characteristic (ROC) curve of low CA-125 level as diagnostic test for ectopic pregnancy

Table 3. Validity indication of serum CA-125 level for diagnosis of ectopic pregnancy.

	cut point of CA-125 (IU/ml)				
	≤ 26	≤ 28	≤ 30	≤ 32	≤ 34
Sensitivity (%)	60	66.7	73.3	80	86.7
Specificity (%)	73.3	73.3	73.3	70	56.7
NPV (%)	64.7	68.1	73.3	77.7	80.9
PPV (%)	69.2	71.4	73.3	72.7	66.7
LR+	2.2	2.5	2.7	2.6	2.0
LR-	0.5	0.4	0.3	0.2	0.2
Accuracy (%)	73.1	73.2	73.3	70.2	57.3

Discussion

In our study, the mean serum CA-125 level in ectopic gestation was significant lower than normal gestation. It was consistent with some previous reports which demonstrated lower serum CA-125 in ectopic pregnancy group[11,12]. Nevertheless, some studies have been failed to demonstrate the difference of CA-125 level between ectopic and normal pregnancy[7]. For some unclear reason, it might be due to the difference in clinical presenting symptom, especially vaginal bleeding in ectopic gestations that affected serum CA-125 level[11], which had been found only 11.7% in this study.

However, there was no significant different of CA-125 level between unruptured and ruptured ectopic pregnant women in the current study[13]. This result was inconsistent to the results of several studies in term of the median CA-125 level in ruptured ectopic pregnancy that was higher than unruptured ectopic pregnancy[8,14,15]. It was not surprising that CA-125 can elevate from peritoneal irritation and destruction of decidua tissue which occurred in ruptured event more than unrupture one. The explanation of indifference of CA-125 level between the two groups in our study might be due to similarly percentage of positive peritoneal fluid in both groups. Moreover, the receiver operating characteristic (ROC) analysis, comparing ectopic pregnancy versus normal pregnancy group, the ROC curves demonstrated a significant discriminatory ability of decreased CA-125 levels for diagnose ectopic pregnancy and the cut-off point of this study was CA-125 level of equally or less than 30 IU/ml., which had the highest efficiency of test. Similar findings have previously been reported[12]. Although each study found different cut-off level with different accuracy, almost all conclude that CA-125 measurement can predict ectopic pregnancy[8,12]. In addition, the NPV in this study was higher than in the previous study[12]. In this study, we decided to choose a cut-off value of 30 IU/ml not only because it had the greatest accuracy but it gave a high negative predictive value also, that has obvious clinical usefulness for a life threatening condition such as ectopic pregnancy.

Conclusion

The measurement of serum CA-125 levels may be useful in discriminating ectopic from normal intrauterine pregnancy.

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ซีรั่ม CA-125 ในสตรีตั้งครรภ์ปกติไตรมาสแรก และสตรีตั้งครรภ์นอกมดลูก

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วัตถุประสงค์ *: เพื่อเปรียบเทียบระดับซีรั่ม CA-125 ระหว่างสตรีตั้งครรภ์ปกติในมดลูกช่วงไตรมาสแรกกับสตรีตั้งครรภ์นอกมดลูก และหาค่าจุดตัดที่เหมาะสมเพื่อใช้ในการวินิจฉัยการตั้งครรภ์นอกมดลูก*

วิธีดำเนินการวิจัย *: งานวิจัยนี้เป็นการศึกษาแบบ cross-sectional ระหว่างเดือนธันวาคม พ.ศ.2555 ถึงเดือนกันยายน พ.ศ.2556 ที่ภาควิชาสูติศาสตร์-นรีเวชวิทยา คณะแพทยศาสตร์วชิรพยาบาล มหาวิทยาลัยนวมินทราธิราช โดยเปรียบเทียบระดับซีรั่ม CA-125 ระหว่าง 2 กลุ่ม แบ่งกลุ่มการศึกษาออกเป็น 2 กลุ่ม คือ กลุ่มสตรีตั้งครรภ์ปกติในมดลูกที่มาฝากครรภ์ และกลุ่มสตรีที่ได้รับการวินิจฉัยว่าตั้งครรภ์นอกมดลูก และต่อมามีผลพยาธิวิทยายืนยัน โดยทำการเจาะเลือดส่งตรวจระดับซีรั่ม CA-125 พร้อมการตรวจเลือดคัดกรองตามมาตรฐานในการฝากครรภ์ครั้งแรกสำหรับสตรีตั้งครรภ์ปกติไตรมาสแรกและตรวจวัดระดับซีรั่ม CA-125 พร้อมการตรวจเลือดเพื่อเตรียมตัวผ่าตัดสำหรับสตรีตั้งครรภ์นอกมดลูก ซึ่งผลการตรวจระดับซีรั่ม CA-125 ของทั้งสองกลุ่มจะถูกนำมาเปรียบเทียบ และหาค่าจุดตัดที่เหมาะสมเพื่อใช้ในการวินิจฉัยการตั้งครรภ์นอกมดลูก*

ผลการวิจัย *: จากสตรีตั้งครรภ์ปกติจำนวน 30 คน และ สตรีตั้งครรภ์นอกมดลูกจำนวน 30 คน ไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติระหว่างทั้ง 2 กลุ่มในแง่ของอายุ จำนวนการตั้งครรภ์ และอายุครรภ์ ส่วนระดับซีรั่ม CA-125 ในกลุ่มสตรีตั้งครรภ์นอกมดลูก (24 ± 10 IU/ml) ต่ำกว่าในกลุ่มสตรีตั้งครรภ์ปกติ (48 ± 36 IU/ml) อย่างมีนัยสำคัญทางสถิติ (P-value เท่ากับ 0.02) เมื่อใช้ระดับซีรั่ม CA-125 ที่ 30 IU/ml เป็นจุดตัดในการวินิจฉัยการตั้งครรภ์นอกมดลูก พบว่ามีค่าความไวร้อยละ 73.3 และความจำเพาะร้อยละ 73.3*

สรุป *: การตรวจระดับซีรั่มCA-125 อาจมีประโยชน์ในการช่วยวินิจฉัยแยกการตั้งครรภ์นอกมดลูกออกจากการตั้งครรภ์ปกติในมดลูก*