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Serum CA-125 as a predictor in the early diagnosis of ectopic pregnancy in Vietnam – A case-control study

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ABSTRACT

Introduction: This study aimed to determine the predictive value of cancer antigen-125 (CA-125) in combination with serum beta-human chorionic gonadotropin (β-hCG) and progesterone in the early detection of ectopic pregnancy (EP).
Methods: Between May 2019 and May 2020, the cross-sectional study recruited 42 cases of EP and 42 cases of IUP at the same gestational age who visited the Department of Obstetrics and Gynecology, Hospital of Hue University of Medicine and Pharmacy. EP was diagnosed based on surgical (laparoscopy) and postoperative pathology examination.
Results: There were significant differences of mean level of β-hCG (2570 mUI/mL vs. 18357.7 mUI/mL), progesterone (10.79 ± 8.16 ng/ml vs. 27.42 ± 4.17 ng/ml) and CA-125 (26.90 ± 10.26 U/mL vs. 70.61 ± 20.89 U/mL) between the EP and the IUP groups ($p < 0.001$). In the prediction of early diagnosis of EP, the cut-off value of CA-125 at 30.94 U/mL has a sensitivity of 89.3% and a specificity of 87,9%; the cut-off value of β hCG at 2750mIU/ml has the sensitivity of 75%, specificity of 78,8%; the cut-off value of progesterone at 10.24 ng/mL has the sensitivity of 85.7%, specificity of 81.8%. A combination of CA-125, β hCG, and progesterone had a sensitivity of 92.8% and a specificity of 90.9% in early diagnosis of EP.
Discussion: Serum CA-125 levels can be used independently or in combination with other markers in the early diagnosis of EP.

Consent for publication

All authors are with consent for publication.

Availability of data and material

The dataset used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

TTNB, CNT, NVQH, LMT developed the study concept and designed the study; TTNB, TTLG and TML collected the data for analysis; TTNB, CNT, NTTN, LMT performed the statistical analysis and drafted the first manuscript; All authors contributed to the interpretation of the data and provided critical revision for important intellectual content. All authors reviewed and approved the final manuscript.

1. Introduction

An ectopic pregnancy (EP) occurs when the growing blastocyst implants outside the lining of the uterine cavity. This disorder is common in obstetric emergencies and is the primary cause of maternal mortality in the first trimester. EP occurs in 1–2% of pregnancies in developed countries but is significantly more prevalent in developing countries [1–3].

Symptoms of EP are extraordinarily varied and not usually predictable. Abdominal discomfort and vaginal bleeding can overlap with intrauterine pregnancy (IUP) symptoms or threatened miscarriage, complicating diagnosis and prognosis [2,3]. As a result, the laboratory is

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critical and crucial in the early diagnosis of EP.

Diagnosis of EP is based on a combination of transvaginal ultrasonography and quantitative serum β-human chorionic gonadotrophin (β-hCG) concentrations [3–5]. While ultrasonography is highly dependent on factors such as the technician's experience and the device's quality, blood parameters, in contrast to subjective parameters, might increase the rate of proper diagnosis. However, diagnosis is frequently delayed because these tests are time-consuming and costly, both psychologically and financially, for medical services. Therefore, finding a biomarker that can differentiate an EP from intrauterine implantation is critical.

So far, over 20 serum biomarkers have been developed to facilitate earlier detection of EP, prompt intervention, and reduce healthcare expenditures [6,7]. Cancer antigen-125 (CA-125) is a cell-surface antigen derived from the coelomic surface epithelium, including the mucosa of the entire female genital tract and maternal decidua. The fetal chorion, amniotic fluid, and maternal decidua all contain considerable amounts of CA-125 and are, therefore, likely origins of elevated serum levels of the protein in pregnancy, which peak around the tenth week [6,7]. This increase was attributed to the trophoblast's infiltration during placental development [8].

Numerous investigations conducted worldwide demonstrated that serum CA-125, β-hCG, and progesterone levels were significantly lower in individuals with EP than in IUP [9,10,12,13].According to Meena et al. (2012), CA-125 levels under 20.5 U/mL, β-hCG levels under 104.5 mUI/mL, and progesterone under 5 ng/ml are considered limiting values in the diagnosis of EP with a sensitivity of 75–86.8% and a specificity of 100% [9]. Similarly, according to Stephen et al. (2013), CA-125 levels under 11.4 U/mL, β-hCG under 3736 mUI/mL, and progesterone under 44 ng/ml contribute diagnosis of EP with a sensitivity of 58–100% and a specificity of 70–85% [10].

Currently, there is no consensus regarding each parameter's cut-off point and diagnostic value, especially CA-125. More researches on the significance of CA-125 in the early detection of EP, either as a sole predictor or in combination with β-hCG and progesterone, are critical and will contribute significantly to the medical literature.

2. Methods

Between May 2019 and May 2020, the study group included pregnant women diagnosed with EP and undergoing surgical treatment at the Department of Obstetrics and Gynecology, together with average pregnant women with a gestational age of fewer than ten weeks, were admitted to the Department of Obstetrics and Gynecology, Hue University of Medicine and Pharmacy Hospital, were enrolled into the study.

The control group consisted of women with normal IUP who received antenatal treatment in the outpatient clinic of the Department of Obstetrics and Gynecology at the same time as patients in the control group.

In this case-control study, the criteria for selection of the study group are pregnant women who satisfied all conditions: (1) were diagnosed with EP based on clinical symptoms and transvaginal ultrasound, (2) were managed by surgical intervention (laparoscopic/open surgery) and (3) postoperative pathology confirmed the presence of placental and trophoblastic cells. Transvaginal ultrasound primarily confirmed the EP diagnosis (a gestational sac with a yolk sac or embryo located in the appendages, a mass with or without a hypoechoic area separate from the ovary) [3,5]. A positive pregnancy test (serum βHCG) with a typical history and characteristics, such as abdominal pain, soreness on pelvic examination, distended lower abdomen, adnexal mass, and a disproportionately small uterus, played a part. Laparoscopy was utilized to diagnose and manage precisely. The control group included pregnant women with an intra-uterine singleton and a gestational age of fewer than ten weeks. In our study, the last menstrual period reported by the pregnant woman is used to estimate the gestational age.

Exclusion criteria included cases of EP in the scar from a previous cesarean section, EP in conjunction with IUP, and comorbidities linked with elevated CA-125 levels such as ovarian tumors, endometriosis, peritonitis, pelvic inflammatory diseases, fibroids, multiple pregnancy cases or multiple pregnancy cases.

2.1. Test-performing techniques

After obtaining informed consent, each pregnant woman was interviewed for the following information: demographic characteristics, menstrual and obstetrical history, and medical or surgical history. The last menstrual period reported by pregnant women is used to estimate the gestational age at an early stage. In cases with irregular menstrual cycles, the previous exam or the results of the most recent ultrasound were used as references. All women underwent venipuncture, and blood was taken during their initial laboratory check for the first visit after administration (for suspected EP) or prenatal care (for IUP). Blood biochemical data (β-hCG, Progesterone, and CA-125) are often available around 2 h following blood collection. Blood samples were centrifuged at 3000 rpm, and serum was stored at −20 °C. The levels of human Chorionic Gonadotropin (hCG), CA-125, progesterone, and estradiol were measured using the monoclonal antibody Enzyme Linked Immunosorbent Assay (ELISA) techniques with the 2010 Elecsys kit (Roche's Cobas 6000).

2.2. Surgical techniques

Laparoscopic surgery can be performed in either a conservative or radical manner. An incision was made in the fallopian tube for a conservative salpingostomy, and the EP was extracted. The EP was identified using laparoscopic forceps, and the tube was immobilized. To reduce bleeding, a 22-gauge needle was inserted through a 5 mm portal to inject a vasopressin solution into the Fallopian tubal wall at the location of greatest distention. Along the tube covering the EP, a 10 mm longitudinal incision was produced using electrosurgery or scissors. The tube contents were extracted using a combination of hydro dissection with the irrigating solution at high pressure and gentle blunt dissection with a suction irrigator. This procedure was also helpful in removing large sections of placental tissue. The tube was then thoroughly cleaned and inspected for coagulation. Bleeding sites may be controlled with pressure or coagulated with a light application of bipolar coagulation.

Besides, a total or partial salpingectomy of the tube containing the EP may be performed. Partial or total salpingectomy is indicated based on the patient's age, the number of tubes present, the tube's condition, and future reproductive wish [1,2,5].

2.3. Data analysis

The data were processed using the Statistical Package for the Social Sciences (SPSS) Version 20.0 program and Excel 2016. The receiver Operator Characteristic (ROC) curve was created to show sensitivity against the specificity of low CA-125 as a diagnostic test for EP. The cut-off value of significant sensitivity and specificity was determined. Subsequently, positive (PPV) and negative predictive values (NPV) were calculated. The area under the ROC curve (AUC) measures a test's accuracy to compare diagnostic deals between tests. A p-value of less than 0.05 was considered statistically significant.

3. Results

This study enrolled 42 cases of EP (study group) and 42 cases of IUP (control group). As shown in Table 1, the mean maternal age (27.74 ± 4.55 vs. 27.17 ± 3.97 or 38.07 ± 4.04 vs. 38.14 ± 2.41), gravidity (2.58 ± 0.68 vs. 2.82 ± 0.82), and gestational age in two subgroups (<6 and ≥ 6 weeks) did not differ statistically significantly between the ectopic and intrauterine groups ($p > 0.05$).

Table 1
Distribution of study individuals by age, gravidity and gestational age between the ectopic and intrauterine pregnancy groups.

Characteristics		Ectopic pregnancy		Intrauterine pregnancy		p-value
		n (%)	Mean ± SD	n (%)	Mean ± SD	
Maternal age (years)	<35	27 (64.3)	27.74 ± 4.55	35 (83.3)	27.17 ± 3.97	p > 0.05
	≥35	15 (35.7)	38.07 ± 4.04	7 (16.7)	38.14 ± 2.41	
Gravidity	Nulliparous	13 (31)	1	14 (33.3)	1	p > 0.05
	Multiparous	29 (69)	2.58 ± 0.68	28 (66.7)	2.82 ± 0.82	
Gestational age (weeks)	<6	22 (52.4)	4.64 ± 0.57	23 (54.8)	4.48 ± 0.52	p > 0.05
	≥6	20 (47.6)	6.79 ± 0.96	19 (45.2)	6.74 ± 0.93	

A comparison of β-hCG, progesterone, and CA-125 concentration between the two groups is shown in Table 2. The change in CA-125 levels was not statistically significant according to gestational age (the subgroup <6 weeks and the subgroup ≥ six weeks) in the group with EP, 26.52 ± 12.51 U/ml and 27.09 ± 9.19 U/ml, respectively, with $p > 0.05$. Meanwhile, in the group of IUP, CA-125 levels gradually increased with gestational age, reaching 58.76 ± 13.49 U/ml in subgroup <6 weeks and 84.93 ± 19.40 U/ml in subgroup ≥ six weeks, respectively, with $p < 0.001$.

In both groups of ectopic and IUP, the change in β-hCG levels was statistically significant according to gestational age (subgroup <6 weeks and subgroup ≥ six weeks, respectively): 3678.46 ± 4845.65 mUI/ml and 17088.86 ± 13435.13 mUI/ml in the group of EP; and 9168.10 ± 18236.21 mUI/ml and 53534.74 ± 45915.95 mUI/ml in the group of IUP.

The decrease in progesterone levels was not statistically significant relative to gestational age in the group with EP, 12.38 ± 8.56 ng/ml and 9.99 ± 7.99 ng/ml, respectively, with $p > 0.05$. Meanwhile, in the group of IUP, progesterone levels gradually increased with gestational age, reaching 25.04 ± 2.62 ng/ml in subgroup <6 weeks and 30.31 ± 3.91 ng/ml in subgroup ≥ six weeks, respectively, with $p < 0.001$.

Table 3 summarizes the predictive value of CA-125, β-hCG, and progesterone in the early detection (less than six weeks gestational age) of EP. CA-125, β-hCG, and progesterone had cut-off values of 30.94 U/ml, 2570 mUI/ml, and 10.24 ng/ml, respectively. CA-125 had a ROC area of 0.912 ($p < 0.001$), a confidence interval of 0.881–0.999, and a 95% threshold of significance of 0.881–0.999 (Fig. 1). Sensitivity is 89.3%, specificity is 87.9%, PPV is 86.2%, NPV is 90.6%, and accuracy is 88.5% at the cut-off point of 30.94 U/mL.

Fig. 2 presents the ROC curve for the β-hCG value in the early detection of EP. The area under the receiver operating characteristic curve is 0.892, $p < 0.001$. The confidence interval with a 95% significance level was 0.875–0.969. A β-hCG cut-off value of 2570 mUI/mL with a sensitivity of 75%, specificity of 78%, PPV of 75%, NPV of 78%, and accuracy of 67.1%.

The ROC curve for progesterone in the early detection of EP is shown in Fig. 3. The area under the ROC curve for progesterone is 0.904 with $p < 0.001$; the 95% confidence interval was 0.855–0.975. At the progesterone cut-off point of 10.24 ng/ml, the sensitivity was 85.7%, the specificity was 81.8%, the PPV was 80%, the NPV was 87.1%, and the accuracy was 83.6%.

Fig. 4 presented the ROC curve for the CA-125 value in combination with β-hCG and progesterone in the early detection of EP. At a combined threshold of β-hCG ≤2570 mUI/ml, progesterone ≤10.24 ng/ml, and CA-125 ≤ 30.94 U/ml, the sensitivity is 92.8%, specificity is 90.9%, PPV

Table 3
Predictive values of tests for predicting ectopic pregnancy at fewer than 6 week pregnancy.

	CA-125	β-hCG	Progesterone	Three marker combination
Cut-off point	30.94 U/ml	2570 mUI/ml	10.24 ng/ml	
Sensitivity	89.3%	75%	85.7%	92.8%
Specificity	87.9%	78.8%	81.8%	90.9%
PPV	86.2%	75%	80%	89.9%
NPV	90.6%	78.8%	87.1%	93.8%
Accuracy	88.5%	67.1%	83.6%	91.8%

CA-125: carcinoma antigen; hCG: human chorionic gonadotropin; PPV: positive predictive value; NPV: Negative predictive. Value.

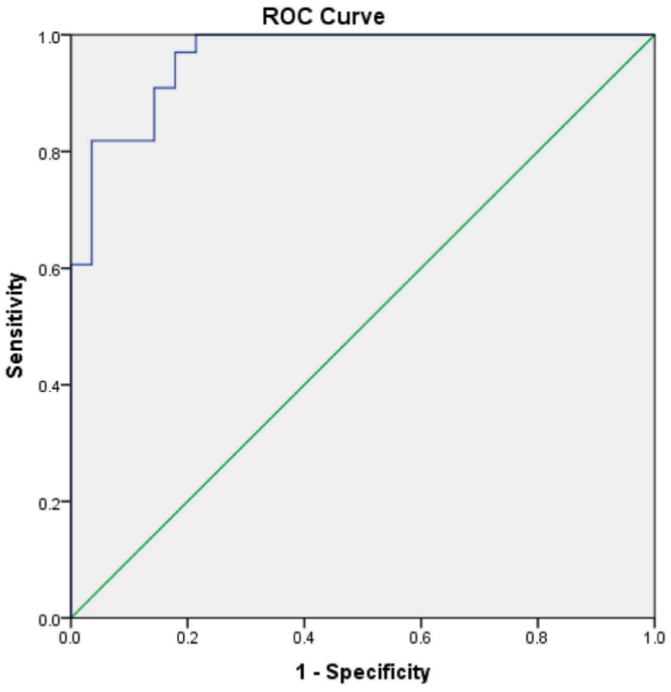

Fig. 1. ROC curve of serum CA-125 level in early diagnosis of ectopic pregnancy.
CA-125 had a ROC area of 0.912 ($p < 0.001$), a confidence interval of 0.881–0.999, and a 95% significance threshold of 0.881–0.999. Sensitivity is 89.3%, specificity is 87.9%, PPV is 86.2%, NPV is 90.6%, and accuracy is 88.5% at the cut-off point of 30.94 U/mL.

Table 2
Comparison of serum β-hCG, progesterone and CA-125 concentration between ectopic and intrauterine pregnancy groups.

Biomarkers	Gestational age <6 week			Gestational age ≥6 week		
	Ectopic pregnancy	Intrauterine pregnancy	p-value	Ectopic pregnancy	Intrauterine pregnancy	p-value
β-hCG (mUI/mL)	3678.46 ± 4845.65	17088.86 ± 13435.13	p < 0.001	9168.10 ± 18236.21	53534.74 ± 45915.95	p < 0.001
Progesterone (ng/mL)	12.38 ± 8.56	25.04 ± 2.62	p < 0.001	9.99 ± 7.99	30.31 ± 3.91	p < 0.001
CA-125 (U/mL)	26.52 ± 12.51	58.76 ± 13.49	p < 0.001	27.09 ± 9.19	84.93 ± 19.40	p < 0.001

Data were presented as Mean ± Standard Deviation.

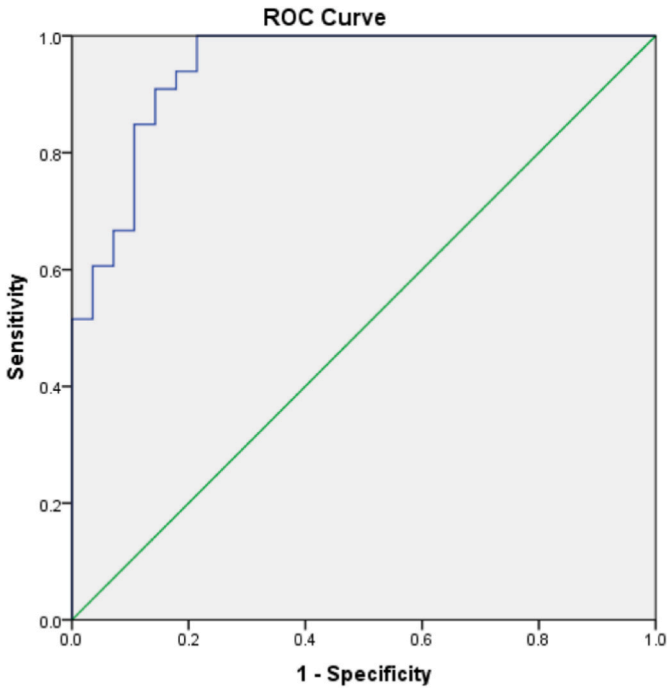

Fig. 2. ROC curve of β-hCG value in early diagnosis of ectopic pregnancy.
The area under the receiver operating characteristic curve is 0.892, $p < 0.001$. The confidence interval with a 95% significance level was 0.875–0.969. β-hCG cut-off value of 2570 mUI/mL with a sensitivity of 75%, specificity of 78%, PPV of 75%, NPV of 78%, and accuracy of 67.1%.

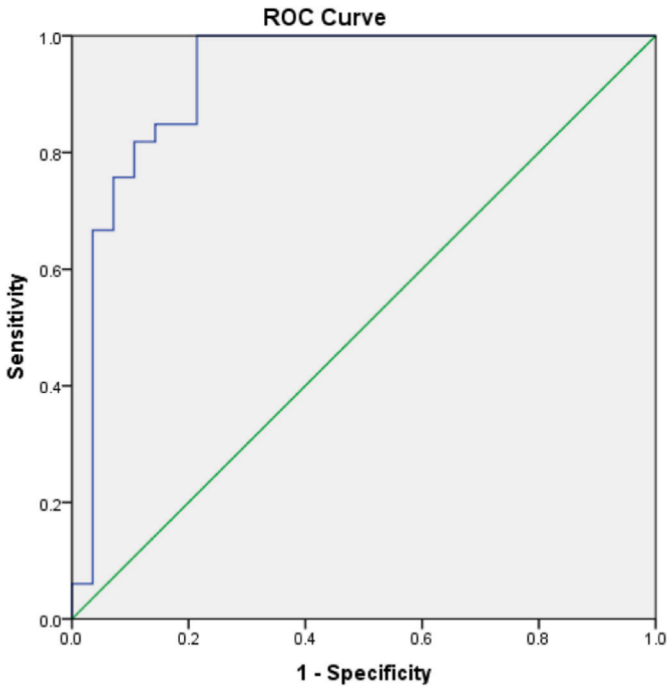

Fig. 3. Progesterone value ROC curve in early diagnosis of ectopic pregnancy.
The area under the ROC curve for progesterone is 0.904 with $p < 0.001$; the 95% confidence interval was 0.855–0.975. It had a sensitivity of 85.7%, a specificity of 81.8%, a PPV of 80%, a NPV of 87.1%, and an accuracy of 83.6% at the progesterone cut-off point of 10.24 ng/ml.

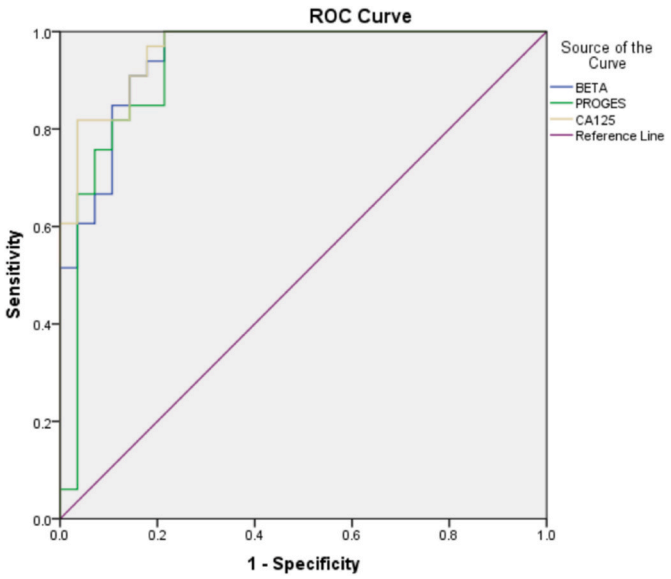

Fig. 4. ROC curve of CA-125 value combined with β-hCG and progesterone in early prediction of ectopic pregnancy.
At a combined threshold of β-hCG ≤2570 mUI/ml, progesterone ≤10.24 ng/ml, and CA-125 ≤ 30.94 U/ml, the sensitivity is 92.8%, specificity is 90.9%, PPV is 89.9%, NPV is 93.8%, and accuracy is 91.8% for ectopic pregnancy prediction.

is 89.9%, NPV is 93.8%, and accuracy is 91.8% for EP prediction.

4. Discussion

Despite improved diagnostic methods that enable early identification and treatment, bleeding from EP remains the critical cause of maternal mortality during the first trimester, accounting for 4% of all pregnancy-related deaths [1,2,11]. Therefore, they should be diagnosed promptly to begin therapy. Adopting a single-point prediction biomarker to identify early EP would facilitate diagnosis at the initial presentation, allowing for medical intervention before life-threatening tubal rupture, hence contributing to the reduction of maternal mortality.

In our study, the mean serum CA-125 level was significantly lower in EP than in IUP. It was consistent with earlier data indicating that EP had decreased serum CA-125 levels. The mean CA-125 concentration in the EP group was 26.90 ± 10.26 U/mL, while 70.61 ± 20.89 U/mL in the early pregnancy group with a statistically significant difference ($p < 0.001$). Different CA-125 concentrations in cases of EP have been reported in previous studies. Some authors found a lower mean CA-125 concentration, ranging from 16.51 ± 2.39 U/mL [9], 15 U/mL [10] to 21.1 U/mL [12], or 24 U/ml [13]. In contrast, greater CA-125 concentrations were found in EP, such as 33 ± 2.5 U/mL [14], 34.58 ± 27.86 U/ml [15], 32.4 ± 20.1 U/ml [16], and up to 38.11 ± 28.79 U/ml [17]. The differences between the studies mentioned above may be attributed to the diverse methods used to choose research patients regarding gestational age and time to surgical indications. In addition, the variance in clinical presentation, particularly vaginal bleeding in ectopic pregnancies, may have also affected the serum CA-125 level [18,19].

The endometrial glands in the decidua are the source of serum CA-125 levels in pregnant women. During pregnancy, maternal serum CA-125 levels may fluctuate. They significantly increase during the first trimester before returning to normal levels throughout the second and third trimesters [20,21]. It has been proven that damage to the decidua and fetal membranes increases maternal serum CA-125 levels. The dynamics and comparison of maternal serum CA-125 levels in IUP, ruptured or unruptured tubal ectopic pregnancies, are inconsistent [22,23]. Certain studies have attempted to establish CA-125 as a diagnostic marker for EP because EP results in a lower CA-125 level than IUP due to

the placenta's inability to grow normally [24,25].

According to our study, the median β-hCG concentration was 2570 mUI/mL in the EP group and 18357.5 mUI/mL in the IUP group. There was a statistically significant difference in concentration between the two groups ($p < 0.05$). This result is greater than the value reported by Meena et al., which was 72.75 mUI/mL in the group EP [9]. In contrast, Katsikis et al. found that serum β-hCG levels were8680.9 mUI/mL in ectopic pregnancies compared to intrauterine pregnancies was 66930.9 mUI/mL [15]. This discrepancy exists because our study subjects are surgical candidates, and the mean gestational age is higher than that of other authors, resulting in a higher β-hCG value.

The average progesterone concentration was 10.79 ± 8.16 ng/ml in the EP group, while 27.42 ± 4.17 ng/ml in the early pregnancy group; this difference is statistically significant $p < 0.001$. This result is higher than that reported by Meena et al., which is 2.54 ± 0.47 ng/ml in the EP group [9]. Nonetheless, Rausch et al. observed that the progesterone levels in EP and IUP were 4.05 ng/ml and 19.05 ng/ml, respectively [22]. Katsikis et al. found that serum progesterone levels in ectopic and intrauterine pregnancies were 7.9 ng/ml and 15.9 ng/ml, respectively [15]. This discrepancy can be explained by our study's higher mean gestational age than the other authors.

At the CA-125 cut-off value of 30.94 U/mL, our study's sensitivity values were all higher than those of the prior studies, and the majority of specificity value was more significant than those of other authors. However, this result was lower than that of the survey conducted by Meena et al. [9]' and the CA-125 cut-off point is also different in the studies (Table 4). It demonstrates that a range of pregnancy-related variables affects the CA-125 levels.

Our cut-off point of β-hCG of 2570 mUI/mL, which was greater than that used by Meena et al. but lower than that used by Stephen et al. [9,10] Accordingly, Stephen et al.'s work included 175 IUP women and 26 women with EP, β-hCG demonstrated 100% sensitivity, 76% specificity, 39% positive predictive value, and 100% negative predictive value for EP at a cut-off of ≤3736 mIU/ml [10]. Meanwhile, Meena et al. used a β-hCG cut-off value of 104.5 mIU/ml for diagnosing EP in the control group; sensitivity was 75%, specificity 100%, PPV was 100%, and NPV was 86% [9].

According to our investigation, with the 10.24 ng/ml cut-off point for progesterone, its sensitivity and specificity were significantly greater than in prior studies. Meena et al. conducted a study on 40 pregnant women with ectopic pregnancies and 24 pregnant women with normal pregnancies. They found a sensitivity of 86.8% and a specificity of 100% at a progesterone cut-off point of 5 ng/ml [9]. However, Stephen et al. reported that a 20.4 ng/ml cut-off of only 65% for EP [10]. Rausch et al. showed that the progesterone had a 70% specificity and an 80% sensitivity at a cut-off of 13.2 ng/ml [22].

Combination of β-hCG ≤2570 mUI/mL, progesterone ≤10.24 ng/ml, and CA-125 ≤ 30.94 U/ml, suggesting a good algorithm for early detecting EP with high accuracy, sensitivity 92.8%, specificity 90.9%, positive predictive value 89.9%, and negative predictive value 93.8%. When CA-125 is combined with other tests for the early diagnosis of EP, its sensitivity and specificity are significantly increased compared to when each test is performed alone. As a result, CA-125 is highly beneficial for detecting EP in its early stages.

4.1. Strengths and limitations

All participants' adnexal status was observed and diagnosed by experienced ultrasonographers, and all other possible reasons for increased serum CA-125 levels were excluded from the study. Our data demonstrated statistically significant variations in serum CA-125 levels between patients with EPs and viable IUPs, validating our hypothesis. As far as we know, this is the first controlled study reported in Viet Nam. Low serum CA-125 values, in conjunction with β-hCG and progesterone levels, aid in the early diagnosis of EPs and show the need for early therapy. A relatively homogeneous cohort was created by retrieving data from a single institution with the same medical practices and diagnostic instruments. However, due to the limited sample size, further studies with larger patient populations should be performed to confirm our findings. Consequently, a single CA-125 assay is not useful for diagnosing ectopic pregnancies. CA-125 should only be mentioned as an additional test in diagnosing EP. In conclusion, in addition to the efficacy of β-hCG and progesterone in predicting EP in earlier research, our findings indicated that the CA-125 test is practical as an additional marker in early EP diagnosis.

Table 4
Comparison of cut-off points, sensitivity, specificity, positive predictive value, negative predictive value of CA-125 in early diagnosis of ectopic pregnancy **in different studies**.

Authors	Year of publication	Cut-off point (U/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Meena M. A et al. [9]	2012	20.5	75.7	100	100	71.4
Stephen A.B et al. [10]	2013	11.4	58	85	36	93
Photjana B et al. [13]	2013	30	73.3	73.3	73.3	73.3
Mutlu et al. [12]	2016	39.77	80	87.2	72.9	94
Our study	2020	30.94	89.3	87.9	86.2	90.6

PPV: Positive predictive value; NPV: negative predictive value.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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