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Diagnostic use of CA 125 values measured on the 2nd and 14th days of the menstrual cycle in endometriosis

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Ethics Committee Approval
The study was approved by the Ethics Committee of Dokuz Eylul University (protocol number: 3686-GOA, 07.12.2017).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: This study examines the difference of serum CRP and CA 125 levels between the menstrual and non-menstrual phases of the menstrual cycle (days 2 and 14) and aims to investigate the diagnostic value of these markers for the early diagnosis of endometriosis.
Methods: There were 36 patients in the study group and 30 patients in the control group (n = 66) in this prospective case-control study. The patients in the study group, who were prediagnosed with endometriosis, were tested for serum CA 125 and CRP on the 2nd and 14th days of menstrual cycle preoperatively (during menstruation and non-menstrual phase) and underwent surgery. The women in the control group were patients who visited the outpatient clinic for a regular checkup without any gynecological complaints.
Results: The CA 125 levels were significantly higher on the 2nd day of the menstrual cycle than the 14th day in the study group [108.15 (90.33) U/mL and 58.60 (39.53) U/mL, respectively, $P < 0.001$]. In the control group, the CA 125 levels were also significantly higher on the 2nd day than the 14th day [22.97 (15.42) U/mL and 13.82 (6.82) U/mL, respectively, $P < 0.001$]. When the comparison was made between the CRP levels on the 2nd and 14th day for the study group [4.52 (4.45) mg/L and 2.82 (3.79) mg/L, respectively], the levels were significantly higher on the 2nd day ($P < 0.001$). The difference of CA 125 and CRP levels between the days [for the study group: ΔCA 125 = 49.55(56.89) U/mL, ΔCRP = 1.69(3.45) mg/L and for the control group ΔCA 125 = 9.14 (11.95) U/mL, ΔCRP = 1.42 (4.74) mg/L] were higher for both markers in the study group, and the differences with the control group were statistically significant ($P < 0.001$ for ΔCA 125 and $P = 0.033$ for ΔCRP).
Conclusion: Our data indicates that it may be possible to support the diagnosis with the evaluation of CA 125 levels during different phases of menstruation separately.

Keywords: Endometriosis, CA 125, CRP, Menstrual cycle

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Introduction

Endometriosis is an estrogen-dependent benign gynecological disease, which affects 10% of women in the reproductive period, and is characterized by endometrial glands and stroma outside the uterine cavity. Typical implantation sites of endometriosis are pelvic organs and the peritoneum. It can cause widespread adhesions in the pelvic region, including the intestines, bladder, and ureters. Less frequently, this can be observed in extrapelvic areas, such as incision sites, eyes, or brain [1].

The definitive diagnosis is made by histopathological examination after surgical excision of lesions. Symptoms that best predict the diagnosis are infertility, dysmenorrhea, and chronic pelvic pain [2]. Among these, the most frequently reported symptom is dysmenorrhea.

Endometriosis foci may be observed as widespread or scarcely distributed in the peritoneum during laparoscopy. Nowadays, endometriosis is examined under three categories: peritoneal endometriosis, ovarian endometriosis, and deep adenomyotic nodular endometriosis [3].

Many serum markers have been studied for the noninvasive early diagnosis of endometriosis. However, no indicator with sufficient sensitivity and specificity has been found yet. These include cytokines, such as VEGF, GM-CSF, IL-2, IL-8, IL-15, IL-6, monochemotactic protein-1, interferon-gamma (IF-γ), and tumor necrosis factor (TNF) [4].

In endometriosis, there is a pelvic inflammatory process with the deterioration of immune cell function in the peritoneal region [5]. For this purpose, C-reactive protein (CRP) is a marker that is investigated in the diagnostic approach of endometriosis, similar to other cytokines.

CA 125 is a well-studied marker and is often increased in women with advanced endometriosis. Serum CA 125 values fluctuate during the menstrual cycle; levels are usually highest in the menstrual phase and lowest in the mid-follicular and periovulatory phases [6].

Clinical rectovaginal examinations and imaging modalities, such as USG, MRI, and CT, have diagnostic value only in patients with advanced endometriosis. The limited diagnostic value of imaging modalities in early-stage endometriosis increases the importance of markers to predict early diagnosis.

In patients with endometriosis, the intraperitoneal inflammatory process is expected to reactivate during the menstruation phase of the cycle. Accordingly, CA 125 and CRP values are expected to increase more during the menstrual phase than the rest of the cycle and the difference between the two measurements is expected to increase. The study aims to determine the difference in CRP and CA 125 levels between the menstrual and non-menstrual phases (days 2 and 14) of the cycle and to investigate the diagnostic value of these markers for the early diagnosis of endometriosis.

Materials and methods

This study was a prospective case–control study. The patients were admitted to the Obstetrics and Gynecology Clinic of Dokuz Eylul University School of Medicine between October 2017 and September 2018. The study was approved by The Ethics Committee of Dokuz Eylul University (protocol number: 3686-GOA, 07.12.2017). The case group consisted of patients, who were previously diagnosed with endometrioma and were studied for CA 125 and CRP levels on the 2nd and 14th days of the preoperative menstrual cycle and underwent an operation. The control group consisted of patients without active gynecological complaints or pathologies and who had visited for a routine checkup. These patients were also tested for CA 125 and CRP on the 2nd and 14th days of the cycle as in the case group. Preoperative diagnoses of the case group were confirmed histopathologically in the postoperative period. Patients who had not been diagnosed with endometriosis histopathologically or who had been previously diagnosed with medical treatment were excluded.

The inclusion criteria for the case group required being 15–49 years of age, being in the reproductive period, and a confirmation of the preoperative diagnosis by postoperative histopathology. For the control group, no gynecological pathology was detected among the patients. In this study, 36 patients in the case group and 30 patients in the control group were included.

Signed informed consent forms were obtained from all participants. Necessary measurements were made for all patients on the 2nd and 14th days of the cycle. In addition, another measurement was made after the surgical procedure in the case group. All findings were recorded in the data record form.

CA 125 analysis was performed on Siemens ADVIA Centaur CP (Siemens Healthineers AG, Erlangen, Germany) with original kits (CA 125 II, cat. No. 09427226) using the chemiluminescent immunoassay method. The sensitivity of the test was 2 U/mL and the measuring range of the test was 2–600 U/mL according to the original documentation.

CRP analysis was performed by Beckman Coulter Olympus AU5800 autoanalyzer (Beckman Coulter, Inc. Diagnostics Division, Brea, CA, United States) with original kits (CRP Latex, cat. No: OSR6199, OSR6299) using the immunoturbidimetric method. According to the original documentation, the sensitivity of the test was 0.2 mg/L and the measuring range of the test was 0.2–480 mg/L.

Statistical analysis

The research was not based on a previous study and, therefore, the sample size calculation was not made according to another research. For a medium effect size, in order to reach 80% power with alpha value set as 0.05, each group required at least 30 participants according to our sample size calculations.

Data, such as age, CA 125, and CRP levels of all patients in the case and control groups were evaluated with the Kolmogorov–Smirnov normality test for normal distribution. For non-normal distributed population, non-parametric Mann–Whitney U and Wilcoxon tests were used to compare both groups between each other and within each other, respectively. Without comparing case and control groups, repeated measurements were analyzed (initial and latter measurements of the same serum marker) with variance analysis to detect any statistical difference between measurements. In this study, the ROC curve and the area under the curve (AUC) was calculated to determine the diagnostic performance in endometriosis of CA 125 and CRP levels on the 2nd and 14th day as well as the level

difference between the two phases. Accordingly, sensitivity and specificity were calculated for the tests with appropriate values.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS version 24.0) (IBM, Armonk, NY, United States), and $P < 0.05$ was considered statistically significant.

Results

A total of 66 patients, 36 with endometriosis and 30 controls, were included in the study. The mean age of the patients was 33.06 (7.37) years in the endometriosis group and 27.90 (7.34) years in the control group. The age range of the patients in the endometriosis group was 21–45 years; in the control group, it was 18–45 years.

In the study, the mean CA 125 level measured on the second day of the menstrual cycle in the endometriosis group was calculated as 108.15 (90.33) U/mL, and 22.97 (15.42) U/mL for the control group. The mean CA 125 level measured on the 14th day in the endometriosis group was calculated as 58.60 (39.53) U/mL, while it was 13.82 (6.82) U/mL for the control group (Table 1).

The mean serum CRP level measured on the 2nd day in the endometriosis group was 4.52 (4.45) mg/L and it was 3.44 (5.17) mg/L for the control group. The mean value for the CRP level measured on the 14th day was 2.82 (3.79) mg/L in the endometriosis group and 2.02 (2.27) mg/L in the control group.

Differences in CA 125 and CRP values measured on the 2nd and 14th day of the cycle in both groups were also calculated in the study. This difference was named delta CA 125 (ΔCA 125) and delta CRP (ΔCRP) in our study.

The mean value for ΔCA 125 in the endometriosis group was 49.55 (56.89) U/mL. The mean value for ΔCA 125 in the control group was 9.14 (11.95) U/mL. The mean value for ΔCRP in the endometriosis group and the control group were 1.69 (3.45) mg/L and 1.42 (4.74) mg/L respectively (Table 1).

Table 1: Comparison of CA 125 and CRP levels between the case and control groups on the 2nd and 14th day of the menstrual cycle

CA 125/CRP/ day of menstrual cycle	Cases (n = 36)	Control (n = 30)	*P*-value
CA 125 (day 2)	108.15(90.33)U/mL	22.97(15.42) U/Ml	< 0.001
CA 125 (day 14)	58.60(39.53) U/mL	13.82(6.82) U/mL	< 0.001
CA 125 (delta)	49.55 (56.89) U/mL	9.14 (11.95) U/mL	< 0.001
CRP (day 2)	4.52 (4.45) mg/L	3.44 (5.17) mg/L	0.064
CRP (day 14)	2.82 (3.79) mg/L	2.02(2.27) mg/L	0.571
CRP (delta)	1.69 (3.45) mg/L	1.42(4.74) mg/L	0.033

The Mann–Whitney U test was used to compare CA 125 (day 2 and day 14), CRP (day 2 and day 14), ΔCA 125, and ΔCRP between both groups. In the analysis performed using the Mann–Whitney U test, the values of CA 125 measured on the 2nd and 14th day of the menstrual cycle ($P < 0.001$ and $P < 0.001$, respectively), ΔCA 125, and ΔCRP ($P < 0.001$ and $P = 0.033$, respectively). The differences were found to be statistically significant between both groups. There was no significant difference between the two groups in CRP values measured on the 2nd and 14th days ($P = 0.064$ and 0.571, respectively) (Table 1).

When CA 125 values on day 2 and day 14 were compared in the study and control groups, the level of day 2 was found to be statistically significantly higher ($P < 0.001$) compared to the 14th day. The difference between the 2nd and 14th day CRP measurements in the case group was statistically significant ($P < 0.001$). There was no significant difference ($P = 0.054$) in the CRP measurements of the control group (Tables 2 and 3).

Table 2: Comparison of CA 125 and CRP values on the 2nd and 14th days in the case group (n = 36)

Variables	2nd day	14th day	*P*-value
CA 125	108.15(90.33) U/mL	58.60 (39.53) U/mL	< 0.001
CRP	4.52(4.45) mg/L	2.82 (3.79) mg/L	< 0.001

Table 3: Comparison of CA 125 and CRP values on the 2nd and 14th days in the control group (n = 30)

Variables	2nd day	14th day	*P*-value
CA 125	22.97 (15.42) U/mL	13.82 (6.82) U/mL	< 0.001
CRP	3.44 (5.17) mg/L	2.02 (2.27) mg/L	0.054

In our study, variance analysis was also performed in repeated measurements (blood values on the 2nd and 14th days of the cycle) without discriminating between the case or control groups. According to the analysis, the serum CA 125 level was found to be significantly higher on the 2nd day of the cycle compared to the 14th day in the study sample ($P < 0.001$). Serum CRP levels were higher on day 2 than on day 14, but the difference was not statistically significant ($P = 0.787$) (Table 4).

Table 4: Comparison of CA 125 and CRP values on day 2 and 14 in the whole sample (n = 66)

Variables	2nd day	14th day	*P*-value
CA 125	69.44(79.54) U/mL	38.25(36.97) U/mL	< 0.001
CRP	4.03(4.79) mg/L	2.46(3.19) mg/L	0.787

When the cut-off for the CA 125 level on the 2nd day was set as 35 U/mL, the false positive rate of the test was 13.1%. The false negative rate was 10.7%;the positive predictive value was 91.6%; and the negative predictive value was 83.3% for endometriosis. When the cut-off for the CA 125 level on the 14th day was set as 35 U / mL, the false positivity rate of the test was 0%. The false negative rate was 25%; the positive predictive value was 72.2%; and the negative predictive value was 100% for endometriosis.

According to the ROC curve analysis, the optimal cut-off value for ΔCA 125 was 14.85 U/mL with 80.6% positive predictive value and 80% negative predictive value (AUC: 0.85, $P = 0.047$). The ratio of two values was also evaluated (the ratio of levels on the second and fourteenth days of the cycle, for each parameter). The ROC curve analysis was unable to provide a statistically significant value ($P > 0.05$); therefore, a cut-off was not set (Figure 1 and Table 5). On the other hand, the ROC curve analysis for CRP-related values could not yield a cut-off value with sufficient positive and negative predictive value either ($P > 0.05$) (Figure 2 and Table 6).

Figure 1: ROC curve for CA 125 values

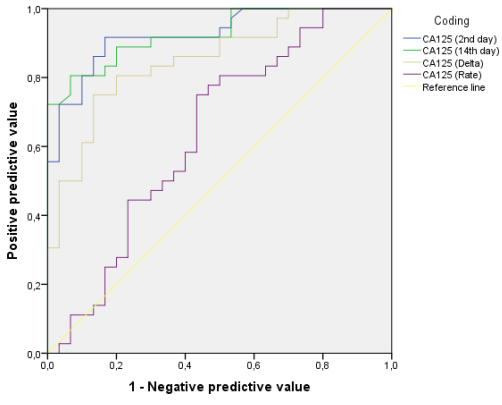

Table 5: Areas under the curve (AUC) on the ROC curve for values using CA 125

CA 125	AUC	95% confidence interval
2nd day	0.93	0.86-0.99
14th day	0.93	0.87-0.99
Delta (Δ)	0.85	0.76-0.94
Rate	0.64	0.50-0.78

Figure 2: ROC curve for CRP values

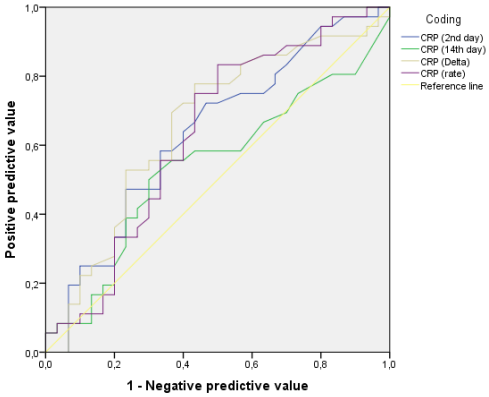

Table 6: Areas under the curve (AUC) on the ROC curve for values using CRP

CRP	AUC	95% confidence interval
2nd day	0.63	0.50-0.77
14th day	0.54	0.40-0.68
Delta (Δ)	0.65	0.20-0.79
Rate	0.63	0.49-0.77

Discussion

Early diagnosis of endometriosis is important. Long-term delays are experienced in diagnosis. In studies conducted for the diagnosis of endometriosis, it was shown that the sensitivity of CA 125 can reach 80% at best, and its benefit in the diagnosis of the disease is limited [7]. According to Oliveira et al. [8], it is possible to increase the sensitivity and specificity of CA 125 in patients with endometriosis when measurements are performed in different periods of the menstrual cycle. In our study, it was determined that the average time between the onset of nonspecific complaints, such as dysmenorrhea and chronic pelvic pain symptoms that may indicate the disease and the diagnosis of endometriosis patients, was four years on average. Even in developed centers, delays of more than six years may occur [9]. Despite the existence of advanced imaging methods, such as transvaginal ultrasonography and MRI, the success in diagnosis is still far from the ideal level because the methods depend on the operator [10, 11].

An effective serum indicator would be useful, as it can easily be standardized and potentially makes screening more accessible. CA 125 is a widely studied serum marker in the diagnosis of endometriosis. According to various comparative studies, other markers have no advantages over CA 125 in the diagnosis of endometriosis. Due to their low sensitivity and specificity, none of the serum markers are accepted as noninvasive diagnostic tests [12, 13].

Menstruation is the most prominent inflammatory phase of the cycle. The measurement of CA 125 during the menstrual period is preferred since the marker is expected to be at its highest level. The reason for fluctuations seen at CA 125 levels during menstruation is thought to be due to endometrial desquamation during menstruation and subsequent short-term deterioration in the tissue blood barrier [14]. By making two measurements, it is possible to evaluate the performance of CA 125 on the 2nd and 14th days and to calculate the difference between these two phases of the cycle.

Some authors have published data on serum CA 125 concentration in spontaneous and stimulated menstrual cycles, revealing that the levels of the marker fluctuate throughout the cycle [15, 16]. In our study, the 2nd day CA 125 levels were significantly higher than the 14th day CA 125 levels in both the case and control groups. This finding supports the belief that CA 125 fluctuates throughout the cycle.

Koninckx et al. [17] evaluated the ratio between two consecutive cycles by studying blood samples taken at the time of menstruation and seven days after (mid-follicular phase). The median value of CA 125 for endometriosis patients was 84 IU/mL in the menstrual phase and 55 IU/mL in the mid-follicular phase. Although the average difference was high (29 IU/mL), the researchers evaluated the menstrual phase/mid-follicular phase ratio to improve the diagnostic power of CA 125, and it was determined that it had no diagnostic potential. In the analysis we performed to measure the diagnostic performance of CA 125 values in our study, we found that the ratio of CA 125 values on the 2nd day and the 14th day did not have a diagnostic function.

In a meta-analysis evaluating CA 125 in the diagnosis of endometriosis, its sensitivity was shown as 28% and specificity as 90% [18]. Our study data gave better results in terms of positive predictive value (91.6%) on the 2nd-day measurement of CA 125, and negative predictive value (100%) on the 14th-day measurement. The diagnostic performance of the difference between the two measurements was not superior. Taking two measurements in different phases of the menstrual cycle raises doubts in terms of cost effectiveness. However, when two measurements in different phases are evaluated separately, it is seen that CA 125 distinguishes sick and healthy people at a higher rate. Thus, better results in terms of cost effectiveness may be obtained by avoiding unnecessary diagnostic procedures.

There are studies on serum CRP levels in patients with endometriosis. In one of these studies, it was shown that CRP was significantly higher in women with advanced-stage (stage 3-4) endometriosis [10]. In another study, no significant difference was found in terms of CRP levels in healthy women with endometriosis [11].

The CRP level measured on the 2nd day in endometriosis patients was found to be significantly higher than on the 14th day. In our study, it was found that the ΔCRP value was statistically significantly different between the two groups. This result shows that CRP may support the diagnosis in endometriosis, but none of the CRP-related values had diagnostic performance for endometriosis.

Limitations

The limitation of the study is that the presence or absence of any pathology was not demonstrated by the diagnostic operation in the patients of the control group.

Conclusion

Our study could not provide any findings that could suggest the use of CRP as a practical parameter for the diagnosis of endometriosis. On the other hand, our research supports the trend in the literature that promotes CA 125 as a valuable parameter for the diagnosis. ΔCA 125 seems to be a potentially helpful marker and future research is expected to further define its use and reliability for both diagnosing the disease and reducing the need for diagnostic surgical interventions.

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