The relationship between ovarian volume and serum CA-125 levels

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Summary

Purpose: The aim of this study was to investigate the relationship between ovarian volume and serum CA-125 levels. *Materials and Methods:* Serum CA-125 levels and ovarian volume were compared among the cases with benign ovarian neoplasms, primary epithelial ovarian cancer (EOC), controlled ovarian hyperstimulation, and ovarian hyperstimulation syndrome (OHSS). Also, the correlation between CA-125 levels and ovarian volume were evaluated in the presence of peritoneal fluid and/or peritoneal carcinomatosis. *Results:* Although ovarian volume was not different among the groups, CA-125 levels were higher in the cases with EOC than with benign ovarian tumors ($p = 0.001$). Baseline CA-125 levels were not found to have increased while ovarian volume went up with controlled hyperstimulation in the infertile group ($p = 0.555$). However, uncontrolled hyperstimulation of the ovaries and the presence of peritoneal fluid caused an increase in the levels of CA-125 ($p = 0.001$). There was no correlation between ovarian volume and CA-125 levels in the cases with malignant ovarian tumors ($r = 0.083$). *Conclusions:* The results of this study have confirmed that CA-125 is a peritoneal marker and increased ovarian volume with benign ovarian neoplasms or controlled hyperstimulation does not increase CA-125 levels in the same way. The presence of peritoneal carcinomatosis and/or peritoneal fluid seems to be an important factor for high CA-125 levels in patients with epithelial ovarian cancer (EOC).

Key words: CA-125; Epithelial ovarian cancer; Peritoneal carcinomatosis; Peritoneal fluid; Ovarian volume.

Introduction

CA-125 is the most commonly used tumor marker for malignant ovarian tumors. It is not only used in the process of diagnosis but also for the follow up of the epithelial ovarian cancer (EOC). Low specificity is the weakest point of this marker. It is very well known that irritation of mesothelial cells of peritoneal, pleural or pericardial surfaces due to inflammatory or malignant conditions is the main cause of increased serum CA-125 levels. However the source of CA-125 is still an open question and its origin may be ovarian, endometrial, peritoneal, or amniotic cells [1]. CA-125 shedding in human peritoneal mesothelial cells has been found to be fivefold higher than ovarian cancer cell lines [2]. So far the majority of the studies have investigated the association between the presence of peritoneal/pleural fluid and CA-125 levels. Although CA-125 is the most commonly used marker in ovarian tumors, there are limited data on the association between the ovarian volume and/or peritoneal fluid on serum CA-125 levels. There are only a few studies evaluating the correlation between CA-125 levels and ovarian volume [3-5]. This study was designed to clarify the relationship between ovarian volume and serum CA-125 levels. For this purpose, serum CA-125 levels were compared among the cases with benign ovarian neoplasm without peritoneal fluid, EOC with or without peritoneal fluid, and large hyperstimulated ovaries with or without peritoneal fluid.

Revised manuscript accepted for publication June 24, 2013

Materials and Methods

This study consisted of 122 patients followed by the Department of Obstetrics and Gynecology, Faculty of Medicine, Cukurova University between June 2010 and March 2012. It was approved by local ethics committee and informed consent was obtained from all patients for participating in the study. Exclusion criteria included a) patients with endometriosis, endometrioma, pelvic inflammatory infection, pregnancy, chronic renal disease, liver disease, cardiac failure, acute lower respiratory system infection, pleurisy, tuberculosis, history of non-gynecologic malignancies, autoimmune disease including systemic lupus erythematosis, rheumatoid arthritis, which are known to increase CA125 level and b) patients with premature ovarian failure, ovarian-paraovarian cysts or neoplasms in the case of infertility, and those who were older than 40 years . Furthermore, the patients with non-epithelioid, mucinous, endometrioid, and pure clear cell type ovarian cancers were excluded.

Patient groups

There were four groups based on the diagnosis. Group 1 consisted of 38 patients with benign ovarian neoplasms, who were evaluated surgically and histopathologically. Of these patients, seven patients had serous cystadenoma, six had mucinous cystadenoma, 15 patients had dermoid cyst, five patients had ovarian fibroma, and five had simple ovarian cyst. Group 2 consisted of 39 patients with EOC, who were categorized according to the FIGO classification system. Six patients were at the early stage (1 and 2) and 33 patients were at the advanced stage (3 and 4) of the disease. The amount of peritoneal fluid was determined during operation and classified as mild (less than one litre), moderate (one to three litres) and massive (≥ four litres). Only one patient had low grade serous carcinoma, and the others had high grade serous (n=33) and serous plus clear cell carcinoma (n=5). Thirty-three patients had peritoneal carcinomatosis and 32 patients had

peritoneal fluid. Group 3 consisted of 34 primary infertile patients who were admitted to infertility clinic and underwent controlled ovarian hyperstimulation (COH) for in-vitro fertilization (IVF). Ovarian volume for these cases was evaluated with transvaginal sonography. The patients in Group 3 received gonadotropins with long luteal protocol. Ovarian volume and CA-125 levels were determined before COH (Group 3-A) and after the hyperstimulation, on the day of human chorionic gonadotropin (hCG) (Group 3-B). Group 4 consisted of 11 patients with moderate to severe ovarian hyperstimulation syndrome (OHSS) classified according to Golan [6]. Group 4 was used as a model for increased ovarian volume and the presence of the peritoneal fluid. Ovarian volume and serum CA-125 levels were determined at admission to the hospital. Ovarian volume was calculated using the prolate ellipsoid formula (L*H*W*0.523) and histomorphometric evaluation methods for Groups 1 and 2. Bilateral ovarian volume was evaluated with two-dimensional ultrasonography and the mean of the bilateral ovarian volume measurements was used in the ovarian volume data in Groups 3 and 4. Serum CA-125 concentrations were analyzed at the central laboratory in the present hospital with chemiluminescent immunoassay kits (OV monitor ref no: 386357).

Statistical Package for Social Sciences (SPSS version 16.0) was used for statistical analysis. Kruskal Wallis and Mann Whitney U tests for non-parametric data were preferred to determine the differences in terms of single and plural comparisons. The comparisons were made using Wilcoxon Signed Ranks test for Group 3 before and after COH. Correlations were assessed through the Spearman Correlation Coefficient test. Data were shown as mean ± SD, median, and min-max value. A significance level of 0.05 (two- sided p values < 0.05) was used in all tests.

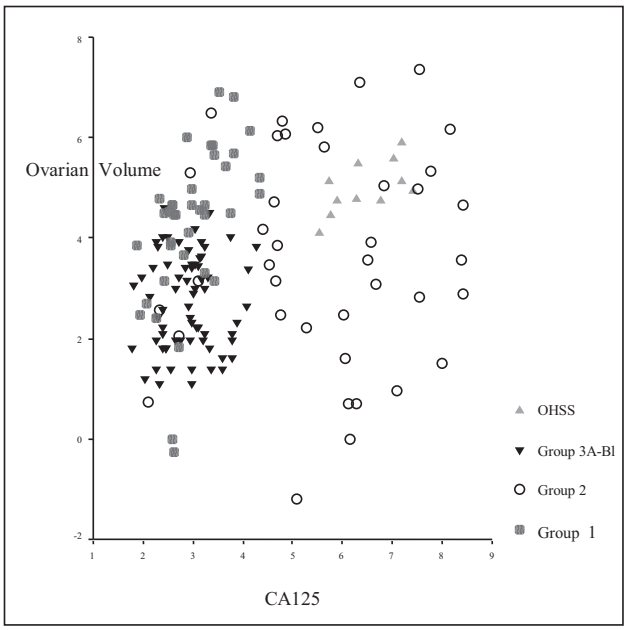

Figure 1. — The scatters graphics of CA- 125 and ovarian volume in the study groups.

Results

There were 122 cases in this study. Mean and median age, ovarian volume, and CA-125 levels and comparison of these variables among the groups are shown in Table 1. Figure 1 shows scatters of CA-125 and ovarian volume for the groups. Serum CA-125 levels were found to be significantly higher in Group 2 than in Group 1 (p = 0.001) although ovarian volume was similar in both groups (p = 0.151). Increased ovarian volume by COH did not change the serum CA-125 levels in the infertile group (p = 0.555). However uncontrolled hyperstimulation of the ovaries and the presence of peritoneal fluid (Group 4) caused an increase in the levels of CA-125 (p = 0.001). Comparisons of serum CA-125 levels and ovarian volume in terms of the presence and amount of peritoneal fluids and peritoneal carcinomatosis are shown in Table 2. The presence of peritoneal fluids and peritoneal carcinomatosis were associated with high levels of CA-125 but ovarian volume was not different among the subgroups.

The correlations of ovarian volume and CA-125 levels in the groups are shown in Table 3. There was a positive but weak correlation between the ovarian volume and serum CA-125 levels in whole group (r = 0.264). This correlation was strong in the group with benign ovarian neoplasms and in the OHSS group (r = 0.548 for Group 1 and r = 0.619 for Group 4). No relationship was observed in the group with ovarian cancer and COH group (r = 0.083 and 0.056, respectively).

Table 1. — *The comparison of ovarian volume and serum CA-125 levels among the study groups.*

	Group 1 (n=38)	Group 2 (n=39)	Group 3A (n=34)	Group 3B (n=34)	Group 4 (n:11)	p
Age (years)	51.0 ± 17	58.3 ± 13.4	30.2 ± 5.4		25.4 ± 2.1	0.001*
	51.5 (18-81)	57 (31-85)	30 (21-40)		25 (22-28)	0.054**
Ovarian volume (cm^3)	164.7 ± 221	193.1 ± 339	7.9 ± 4.5	39.4 ± 23	169.1 ± 92.1	0.001*
	92.5 (1-988)	35 (1-1569)	7.7 (1.8-23)	33 (13-115)	140 (60-374)	0.151**
						0.001***
						0.001****
CA-125 (IU/l)	24.5 ± 17.8	945 ± 1327	21.0 ± 17.2	21.4 ± 13.4	780 ± 494.5	0.001*
	14 (3-64)	414 (8-4509)	14 (3-64)	19.3 (6-71)	547 (256-1632)	0.001**
						0.555***
						0.001****

*: Kruskal-Wallis Test, **: Mann Whitney U Test between Groups 1 and 2, ***: Wilcoxon Signed Ranks test between Groups 3A and 3B, ****: Man Whithney U Test between Groups 3B and 4.

Table 2. — *The comparison of serum CA-125 levels and ovarian volume according to the presence and amount of peritoneal fluids and peritoneal carsinomatosis in ovarian cancer patients.*

	Ovarian volume (cm^3)	CA-125 (IU/l)	*p*
Group 2			
Ascite absent (n=7)	268 ± 223	442.6 ± 851.1	0.368*
	207 (24-563)	122.2 (22-2367)	0.022**
Ascite present-mild (n=12)	280.6 ± 455.3	471.7 ± 583.5	
	57.5 (2-1569)	192 (10-1893)	
Ascite present-moderate (n=9)	221.5 ± 406.9	1821 ± 1835.1	
	18 (1-1230)	560 (194-4509)	
Ascite present-massive (n=11)	26.9 ± 44.4	1064.8 ± 1427	
	12 (1-156)	428 (8-4353)	
Group 2			
Peritoneal carcinomatosis Absent (n:6)	237.9 ± 205.5	355 ± 757.3	0.643*
	200 (24-563)	109 (19-2367)	0.028**
Present (n:33)	179.6 ± 371	1122.1 ± 1417.3	
	20 (1-1469)	497 (8-4509)	

*: Comparison of the ovarian volume, **: Comparison of the CA-125 levels.

Table 3. — *The correlations of ovarian volume and CA-125 levels in the study groups.*

	Group 1 Benign ovarian neoplasm (n=38)	Group 2 Malign ovarian neoplasm (n=39)	Group 3A-B Pre-post induction COH (n=34)	Group 4 OHSS (n=11)	All groups (n=122)
Correlation (ovarian volume-CA-125 levels)	0.548**	0.083	0.056	0.619*	0.264**

* Correlation is significant at the 0.05 level (2-tailed). ** Correlation is significant at the 0.01 level (2-tailed). OHSS: Ovarian hyperstimulation syndrome.

Discussion

This study was designed to investigate the association between serum CA-125 levels and ovarian volume in different patient populations with ovarian enlargement. The study groups included both large neoplastic and non-neoplastic ovaries with or without peritoneal fluid. In the literature review, the authors found only a few studies evaluating the association between CA-125 levels and ovarian volume. Van Altena *et al.*, [3] investigated CA-125 level in the patients undergoing prophylactic bilateral salpingo-oophorectomy (BSO) and found that ovarian volume did not contribute to the levels of CA-125. Granberg *et al*. [4] did not demonstrate a correlation between CA-125 levels and ovarian volume in 106 women with different cycle of phase and in postmenopausal status. The present authors did not find a correlation between ovarian volume and serum CA-125 levels in the patients with EOC. Additionally there was no association between CA-125 and enlarged ovaries by COH. High CA-125 levels were found to be related to EOC and the presence of peritoneal fluids and peritoneal carcinomatosis. These findings suggest that CA-125 is a peritoneal marker.

In the literature review, there is a controversy regarding the relationship between CA-125 and COH. However, in this study the authors did not find an association between serum CA-125 levels and COH. This result shows concordance with the previous report by Vujisic *et al.* [7]. The relationship between CA-125 level and OHSS had been discussed in the literature [8]. For the OHSS group, high levels of CA-125 were found in this study. The present results suggest that the presence of peritoneal fluid may be responsible for elevated CA-125 levels in OHSS.

It is very well known that the presence and amount of the peritoneal fluid and peritoneal carcinomatosis affect the levels of serum CA-125 [9,10]. Topalak *et al.*, [11] reported that high serum CA-125 levels were closely related to the presence of serosal fluids and serosal involvement. In another study, five to six fold higher serum CA-125 levels were found in the ovarian cancer patients with peritoneal fluids as compared with the patients without peritoneal fluids [5]. Considering the results of this study, serum CA-125 levels in the ovarian cancer patients with peritoneal carcinomatosis were approximately six fold higher than in those without peritoneal carcinomatosis and high serum CA-125 levels were closely correlated with the peritoneal extension of the disease. In another study, it was reported that peritoneal carsinomatosis did not play an important role on serum CA-125 levels [10]. The present authors found higher serum CA-125 levels for the patients with peritoneal fluids and peritoneal carcinomatosis than for the patients without peritoneal fluids and/or peritoneal carcinomatosis. This finding suggests that serum CA-125 levels are associated with the presence of the peritoneal fluids and peritoneal carcinomatosis rather than ovarian volume.

It has been shown many times that the levels of CA-125 are related to the stage of the ovarian cancer and some type of histologic subtypes [12]. Peritoneal fluids and peritoneal involvement are more frequent in the cases with advanced stage disease and higher CA-125 levels are found in the cases with serous tumors as compared to other epithelioid or non-epithelioid ovarian cancers. For this reason, the authors included the patients with serous ovarian cancer and excluded the patients with mucinous or other non-epithelioid ovarian cancers. Almost all of our ovarian cancer patients had advance stage disease (33/39), peritoneal carcinomatosis (33/39 and peritoneal fluid (32/39). These results have supposed that the presence and amount of peritoneal fluid and peritoneal carcinomatosis cause high levels of CA-125 in the patients with EOC.

The evaluation of ovarian cancer mass volume has distinct and serious limitations especially for the management of the ovarian cancer patients [13]. There are controversies in the literature on monitoring the ovarian cancer patients with serum CA-125 levels [14-16]. The present study results may contribute to the routine for monitoring serum CA-125 levels in the EOC patients, which can more adequately define the changes in tumor volume associated with small macroscopic and diffuse microscopic cancer.

In conclusion, the presence and amount of not ovarian volume but of peritoneal fluids and peritoneal carcinomatosis are related to serum CA-125 levels in EOC. This finding supports the discordance between CA-125 levels and ovarian volume shown by imaging methods.

Acknowledgement

The authors thank Assoc. Prof. Dr. Gulsah Seydaoglu for the statistical analysis of the study.

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