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ORIGINAL ARTICLE

Evaluation of factors that may be responsible for cyclic change of CA125 levels during menstrual cycle

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Abstract
Objective To evaluate the factors responsible for fluctuation of CA125 levels during menstrual cycle
Methods The study was performed with patients who had undergone hysterectomy for benign gynecological disease (group I, $n = 30$) and patients who had undergone laparoscopy for tubal ligation (group II, $n = 30$) or for investigation of pelvic cause of infertility (group III, $n = 24$) and showed normal laparoscopic findings. In groups II and III, blood samplings for serum CA125 determination were performed in menstrual and no-menstrual period. In group I, sampling times were determined by using estrogen and progesterone levels. Mean serum CA125 concentrations were compared using one-way analysis of variance (ANOVA) for multiple group comparisons and paired t test for within-group comparisons.
Results Intra-individual serum CA125 concentrations of group I was not significantly different ($P > 0.05$). In group II, mean menstrual CA125 concentration was on average 18.2% higher than that of non-menstrual concentration ($P < 0.001$). Group III showed a similar pattern to that of group II, with a difference of 22% ($P < 0.001$). Mean CA125 concentration of group I in both menstrual and non-menstrual period was lower than those of groups II and III ($P < 0.001$). However, there was no significant difference between groups II and III when compared with the corresponding menstrual and non-menstrual CA125 concentrations ($P > 0.05$).
Conclusion Endometrium is responsible for the cyclic changes in serum CA125 concentration during menstrual cycle

Keywords CA125 · Menstrual cycle · Retrograde menstruation

Introduction

CA125 is a high molecular weight glycoprotein expressed on the cell surface of embryonic colemic epithelium. Its presence on the epithelium of the fallopian tubes, endometrium, endocervix, as well as on the peritoneum, pleura and pericardium have been demonstrated [1]. Many authors have reported a data on serum CA125 concentrations throughout the spontaneous or stimulated cycle and demonstrated the fluctuation of CA125 levels during the menstrual cycle [2, 3]. However, less is known about factors involved in this fluctuation. Proliferation of granulosa and theca cells, disintegration of endometrium during menstruation and peritoneal irritation due to seeding of endometrial cell via retrograde menstruation have been proposed [4, 5], but exact mechanism is still unclear (Table 1).

We aimed to evaluate the factors that may influence serum CA125 concentration during menstrual cycle

Materials and methods

Patients with a history of hysterectomy as a part of treatment of benign gynecological disease and patients

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Table 1 CA125 level of groups at menstrual (M) and non-menstrual (NM) periods

	Group I	Group II	Group III	*P*
Age (years)	38 ± 3.5 (34–42)	32 ± 2.5 (30–39)	28 ± 4.6 (18–34)	<0.001**
M CA125 (Uml^{-1})	8.8 ± 2.5 (4.2–15.8)	11.5 ± 4.3 (4.6–18.5)	10.1 ± 4.7 (5.5–24.2)	<0.001**
NM CA125 (Uml^{-1})	8.5 ± 1.5 (3.6–13.5)	13.6 ± 4.5 (6.2–21.5)	12.2 ± 4.8 (5.4–20.5)	<0.001**
P	>0.05*	<0.001*	<0.001*	

Data were presented as mean ± SD (range)

*Paired *t* test for within-group comparison, **ANNOVA for multiple groups comparison

who had undergone laparoscopy for either tubal ligation or investigation of pelvic cause of infertility were inculuded in the study. Group I comprised of 30 women (aged 34–42 years) with no episode of hot flushes and serum FSH < 15 IU, $E_2 > 40$ $pgml^{-1}$ but a history of hysterectomy as a part of treatment of benign gynecological disease. Group II comprised of 30 patients (aged 30–39 years) who showed regular menstrual cycle and underwent laparoscopic tubal ligation. Group III comprised of 24 patients (aged 18–34 years) who showed regular menstrual cycle and underwent laparoscopy for investigation of infertility. All these patients had no evidence of disease that could interfere with the interpretation of CA125 levels such as endometriosis, pregnancy, pelvic inflammatory disease, leiomyoma, tuberculosis, endometrial–tubal or ovarian cancer. At least 3 moths after surgery, blood samplings were performed for serum CA125 determination in menstrual period (days 2–4, since the start of menstruation) and non-menstrual period (days 10–15, since start of menstruation). Since patients with hysterectomy (group I) had no menstrual efflux, sampling times were determined by using estrogen and progesterone levels.

All the serum samples were collected by venipuncture and stored at −35°C until assay. We used the electrochemiluminescence immunoassay (Elecsys® Systems, Roche Diagnostics, Turkey) for CA125 determination. Mean serum CA125 concentrations were compared by one-way analysis of variance (ANOVA) and Scheffe F procedure for multiple group comparisons and paired *t* test for within-group comparisons.

Results

Mean CA125 concentrations of patients with hysterectomy (group I) were 8.8 and 8.5 Uml^{-1} at menstrual and non-menstrual samplings, respectively. Although slight difference was observed between these two measures, it was not statistically significant ($P > 0.05$). Mean CA125 concentrations of women with tubal ligation (group II) in menstrual and non-menstrual period were 13.6 and 11.5 Uml^{-1}, respectively. In this group, mean menstrual CA125 concentration was average 18.2% higher than that of non-menstrual CA125 concentration ($P < 0.001$). The patients with normal laparoscopic finding (group III) showed a similar pattern to that of women with tubal ligation, with a difference of 22% ($P < 0.001$). Mean serum CA125 concentrations of these patients were 12.2 and 10 Uml^{-1} in menstrual and non-menstrual periods, respectively. Mean CA125 concentrations of group I, both in menstrual and non-menstrual period, was lower than those of groups II and III ($P < 0.001$). However, there was no significant difference between groups II and III with respect to corresponding menstrual and non-menstrual CA125 concentrations.

Discussion

There is a controversy about CA125 fluctuation in menstrual cycle. Zeimet et al. [2] reported that the physiological CA125 level is linearly elevating from middle proliferative phase to the early secretory phase, slowly falling during middle secretory phase and rising to the late secretory phase. Jager et al. [6] also suggested that CA125 levels in sera of apparently healthy women depend on the phase of their menstrual cycles. Contrarily, Zweers et al. [3] reported no fluctuation of CA125 levels during spontaneous cycle. In the present study we found significant changes of CA125 serum levels throughout the menstrual cycle in both groups II and III. It seems that mean CA125 concentration are increasing during menstruation when compared to the non-menstrual CA125 levels. On the other hand, women who had undergone hysterectomy showed no CA125 fluctuation.

There is no shared point of view regarding the contribution of endometrium, fallopian epithelium or ovarian epithelium on serum CA125 fluctuation during

menstrual cycle. Jager et al. [6] proposed that in the spontaneous cycles, the follicle is responsible for cyclic release of CA 125 into the systemic circulation. They found that CA125 serum levels are reflecting follicular development, which involves proliferation of theca and granulosa cells, and suggested that CA125 is derived from one of these ovarian components. The opposite results were presented by Mordel et al. [7], who reported that intrafollicular CA 125 secretion is not connected with follicular steroidogenesis. Similarly, Phocas et al. [8] concluded that ovarian steroidogenesis is unlikely to affect ovarian CA 125 production and Jimena et al. [9] did not establish any correlation between gonadotropin and gonadal steroid hormone and CA125 levels.

The hypothesis that ovary is the source of serum CA125 could not be confirmed also in the study of Zeimet et al. [2], who studied the CA125 reactivity of ovarian tissue, fallopian tissue, endometrial tissue and endometrial epithelium in relation to CA125 concentrations and reported that higher tissue concentrations are within the endometrium. Moreover, cyclic changes in the tissue CA125 content are only seen in the endometrium. This led them to conclude that the endometrium is responsible for the cyclic changes in serum CA125 concentration, although the mechanism involved in the shedding of CA125 into the circulation remains to be elucidated. The higher serum CA125 concentration measured in the first trimester pregnancy, and patients with hydatidiform mole, where a great deal changes are taking place within endometrium support this hypothesis. In the present study, since patients who underwent hysterectomy showed no fluctiotion in the presence of functional ovary, we believe that the role of ovarian changes during menstrual cycle has insignificant role in fluctuations of CA125 or it needs the presence of functional endometrium to be effective.

An alternative hypothesis to explain menstrual CA125 fluctuation has been put forward by Kenemans et al. [5]. They claimed that the seeding of endometrial tissue transported via the tubes into the peritoneal cavity result in local inflammatory reaction and subsequent CA125 elevation. In the present study, since we found no difference between serum CA125 concentrations of women with bilateral tubal ligation and those of women with normal tubes, we conclude that tubal reflux could not explain the increase of serum CA125 during menstruation. In line with our result, Check and Vetter [10], who investigated whether the concept of tubal reflux could explain the high level of CA125 observed during the first trimester of pregnancy, found out equal CA125 concentrations in both patients with and without tubal ligation.

In the light of literature and results of present study we conclude that disintegration of endometrium that demolish tissue-blood barrier for a short interval during menstruation may be responsible for fluctuation of CA125 during menstrual cycle, but there might be a point as a possible bias of the interpretation because ruling out of presence of disseminated and minor foci of endometriosis in the pelvic peritoneum in all cases showing fluctuations of CA 125 might have been a difficult task to do even by precise laparoscopy.

References

1. Colacurci N, Fortunato N, De Franciscis P, Fratta M, Cioffi M, Zarcone R, Cardone A (1996) Serum and peritoneal CA-125 levels as diagnostic test for endometriosis. Eur J Obstet Gynecol Reprod Biol 66:41–43
2. Zeimet AG, Muller-Holzner E, Marth C, Daxenbichler G, Dapunt O (1993) Tumor marker CA 125 in tissues of the female reproductive tract and in serum during the normal menstrual cycle. Fertil Steril 59:1028–1035
3. Zweers A, De Boever J, Serreyn R, Vandekerckhove D (1990) Correlation between peripheral CA 125 levels and ovarian activity. Fertil Steril 54:409–414
4. Saraf VK, O'Neill M, Riccioli A, Penha PD, Obasaju MF, Josimovich JB (1995) Correlations between periovulatory serum and follicular fluid CA-125 and granulosa cell hormones after controlled ovarian hyperstimulation. Eur J Obstet Gynecol Reprod Biol. 62:95–99
5. Kenemans P, Bast RC Jr, Yedema CA, Price MR, Hilgers J (1988) CA125 and polymorphic epithelial mucin as serum tumor markers. Cancer Rev 12-12:119–144
6. Jager W, Diedrich K, Wildt L (1987) Elevated levels of CA 125 in serum of patients su.ering from ovarian hyperstimulation syndrome. Fertil Steril 48:675–678
7. Mordel N, Anteby SO, Zajicek G, Roisman I, Treves A, Barak V (1992) CA 125 is present in significant concentrations in periovulatory follicles of in vitro fertilization patients. Fertil Steril 57:377–380
8. Phocas I, Sarandakou A, Rizos D, Dimitriadou F, Mantzavinos T, Zourlas PA (1994) Tumour-associated antigens,CEA, CA 125 and SCC in serum and follicular fuid of stimulated and unstimulated cycles. Eur J Obstet Gynecol Reprod Biol 54:131–136
9. Jimena P, Castilla JA, Ramirez JP, Gil T, Acebal M, Molina R, Herruzo AJ (1993) Follicular fluid alpha-fetoprotein, carcinoembryonic antigen, and CA 125 levels in relation to in vitro fertilization and gonadotropin and steroid hormone concentrations. Fertil Steril 59:1257–1260
10. Check JH, Vetter BH (1995) A challenge to the concept of tubal reflux to explain the rise and fall of CA125 in serum during the first trimester. Hum Reprod 10:674–676