Tr. J. of Medical Sciences
29 (1999) 673-675

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Is The Serum CA125 Level Originating From Endometrum Influenced by Exogenous Estrogen Administration?

Received: January 19, 1998

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Abstract: Objectives: To assess the endometrial contribution of serum CA125 and its influence from estrogen administration in menopausal women.

Desing: A randomised, controlled, prospective study.

Materials and Methods: Twenty menopausal women with intact uterus and ovaries (study group) and ten cases with total hysterectomy were selected through a random table among the referred menopause patients for hormone replacement therapy. Mean ages and menopause lengths of the study and control groups were similar. Ten cases and five controls had 15 days of transdermal 100 µm/d estradiol (TE) (group 2), and similarly the other cases with five controls had estradiol were measured at day same period of time (group 1). Serum CA125 and estradiol were measured at day 0 and by radio immunoassay (RIA). Statistics were analysed by paired and unpaired Student's t test where appropriate.

Results: Serum mean CA 125 levels increased in endometrium intact menopausal women from day 0 to 15 of TE administration in group 2 and 1, 70% and 6% respectively (p=0.03 and 0.05). Serum estradiol accompanied this increase only in group 2 significantly.

Conclusion: Endometrial CA125 secretion to serum is dependent on the dose of exogenous estrogen administered. Th subject population used in this study is a good model to assess the endometrial contribution of serum CA125 with exogenous estrogen administration by ruling out ovarian activity.

Key Words: Endometrial serum CA125, serum estradiol, menopause.

Introduction

It is well known that menopause and hysterectomy are important factors in reducing serum CA125 levels in women. Previously, the endometrial CA125 secretion in vitro has been shown in primary culture of human endometrial stromal cells, its concentration in the medium being significantly higher with cells obtained during the proliferative and early secretory phases compared with those obtained during the late secretory phases (1). However, further studies are warranted to understand the precise effects of estrogen and progesterone on serum CA125 levels in menopausal patients who have had or have not had hysterectomy. Since exogenous estrogen restores the endometrial activity in menopausal women, serum CA125 levels may also show a coupled increase with the increased serum estrogen levels. We report our preliminary findings from a randomised, controlled, prospective study for the assessment of estrogen administration on endogenous serum CA125 levels in menopausal women with and without intact uterus.

Materials ve Methods

Twenty menopausal women with intact uterus and ovaries (study group) and ten cases with previous total hysterectomy (control group) were included in the study. Hysterectomy indications of the controls are outlined in Table 1. Informed consent was obtained from all study subjects and controls, randomly selected from clinic patients by use of a random table. The mean ages of subjects in the study and control groups were similar i.e. 53±1.9 (SD) and 51±2.7 years. The menopause lengths in the study and control groups were also similar i.e. 61.0±18 and 52.6±26.5 months respectively.

Group 1 consisted of ten cases and five controls, randomly selected, who received 15 days of 50µgm/day transdermal 17β–estradiol (TE). Group 2 consisted of a further 10 cases and 5 controls, randomly selected, who had 15 days of transdermal 100µgm/day 17β–estradiol (Estraderm–Ciba) administration. Serum CA125 and estradiol were measured at day 0 and 15 by radio immunoassay (RIA). To prevent inter–assay variability, serum of each case was frozen and counted once. CA125 and estradiol levels were measured using a solid phase RIA with a sensitivity level of 0.5 U/ml (CIS–bio international, France) and 8 pg/ml (DPC–Coat–a–count, Los Angeles, Ca.) respectively. The inter–assay variability was within a CV percentage of 3.2–4.2 for CA125 and 4.2–8.1 for estradiol. Because baseline CA125 levels in menopausal women showed individual differences, CA125 and serum estradiol levels before and after exogenous estrogen administration were compared using the paired t test.

Results

The results are presented in Table 2. In study groups if CA125 levels significantly increased, serum estrogen levels increased as well. In Group 2 100µgm/d TE administration resulted in a 70% CA125 increase on day 15 (p=0.03) with an accompanying increase in serum estradiol levels (p<0.03). In Group 1, 50µgm/d TE administration resulted in a 6% increase in serum CA125 levels at the significance level of p=0.05 with an insignificant concomitant inrease in estrogen levels.

Table 1. The diagnosis of the previous hysterectomised patients in the control group.

Diagnosis	N
Benign myoma uteri	5
Submucous leiomyoma – necrosis	1
Endometrial polyp – necrosis	1
Abnormal vaginal bleeding with atrophic endometrium	1
Abnormal vaginal bleeding with focal hyperplasia	2

Discussion

The major finding of this study is that endometrium intact menopausal women respond to 15 days of 100 µgm/day TE administration with a significant increase (70%) in the serum CA125 level. On the other hand, 15 days of 50 µgm/day TE results in a less significant increase in the serum CA125 level (6%) in this sample size (p=0.05). These findings are consistent with the previous in vitro findings which show that stimulation of endometrial cells causes increased CA125 secretion (2, 3).

A recent review has reported the menstrual cycle–dependent expression of CA125 in normal tissues of the female reproductive tract in relation to the actual circulating CA125 levels, together with in vivo data concerning the inductive effect of medroxyprogesterone acetate on circulating CA125 in 24 post menopausal women (4). The results of our study, where 100µgm/d TE administration resulted in a 70% CA125 increase on day 15 with an accompanying increase in serum estradiol levels, supports the induction hypothesis above.

While CA125 may increase in non-reproductive system related conditions such as mesothelioma, tuberculosis, gastric carcinomas, breast cancer, mainly reproductive system related conditions such as pregnancy, leiomyoma, pelvic inflammatory disease, endometriosis, endometrial–tubal or ovarian carcinoma increase circulating CA125 levels (5). None of the cases in this

Table 2. Serum mean (±SEM) CA125 and estradiol levels in study and control group before and after 15 days of 50–100 µgm/d TE administration in group 1 and 2 respectively.

Day			0	15
CA125	Group 1	Study	17.2±2.5	18.2±2.6 ¶
		Control	17.9±5.8	17.1±5.1
	Group 2	Study	11.6±1.7	19.7±4.1 †
		Control	10.5±1.8	14.3±3.7
S. Estradiol	Group 1	Study	26.7±10.7	86.0±8.7
		Control	25.0±4.5	40.2±6.5
	Group 2	Study	16.3±3.6	140.8±32.8*
		Control	27.7±11.6	125.6±41.8*

(¶= 0.05, †p= 0.03, *p<0.03)

study had been diagnosed with any of these conditions except menopause. All of our mean results among the groups were lower than the tumour cut–off value (<35 U/ml) and were within 10–18 U/ml throughout the study. Previously, hormone replacement therapy in menopause has been shown to increase the baseline mean CA125 levels by 20% where the calculated cut–off value to detect endometrial carcinoma has been reporteD to be 20 U/ml for menopausal individuals (6). Takami (6) and Kurihara (7) found mean CA125 in normal menopausal women to be 5.5 and 10.8 U/ml respectively and advocated that each laboratory should establish its own normal range.

In summary, the results of this study indicate that the serum CA125 level is influenced by the serum blood estrogen level and is dependent on the estrogen dose administered. Thus, in menopause, estrogen replacement therapy may increase the baseline CA125 in relation to the dose of estrogen administered. However, this therapeutic dose of estrogen increases CA125 around 20U/ml, which is far below the cut–off point previously reported (6).

The subject population used in this study is a good model to assess the endometrial contribution of serum CA125 with exogenous estrogen administration by ruling out ovarian activity. However, this study has certain limitations regarding the conclusions to be drawn from the limited sample size. Due to the preliminary nature of the study, the current results reflect our findings without any predetermined sample size and power calculations. Thus, a larger study with a higher sample size may be beneficial for the assessment of the effects caused by 50 µgm/day TE administration on the serum CA125.

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