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## Pronounced Increases in the Concentration of an Ovarian Tumor Marker, CA-125, in Serum of a Healthy Subject during Menstruation

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CA-125 is a glycoprotein associated with various ovarian tumors. A commercial radioimmunoassay involving a monoclonal antibody is available for it. In our laboratory, a normal-value study was conducted as part of a routine evaluation of this assay. One healthy subject had a serum CA-125 concentration >300 kU/L, more than eightfold the upper limit of normal (35 kU/L). This increase, which coincided with the onset of the menstrual period, subsided to within the normal range by the end of the menstrual cycle. The half-life of CA-125, calculated from this decrease, was 6.4 days. Similar observations were made in the same subject over several menstrual cycles. Results of clinical and ultrasound examinations of the subject for ovarian tumors were negative. No clinical evidence of malignancy was present eight months after the initial discovery of an increased CA-125. None of the other 39 healthy subjects had a CA-125 value >51 kU/L. Five of these subjects had CA-125 determined several times during their menstrual cycles; none exhibited pronounced variations in CA-125 concentrations. Evidently CA-125 can be extremely increased in a healthy woman, and possible effects of the menstrual period on serum CA-125 concentrations should be considered in pre-menopausal patients.

**Additional Keyphrases:** *reference interval · biological half-life*

Until recently, there was no effective non-invasive test for following cases of ovarian cancers. Commonly available biochemical tumor markers such as CEA (1, 2) are significantly increased (>5 µg/L) in less than 25% of the cases of ovarian malignancies and thus usually are not satisfactory for following treatment or detecting recurrences. Recently, Cancer Antigen 125 (CA-125) has demonstrated promise as a serum marker for epithelial ovarian malignancies (3). CA-125 is an antigenic determinant associated with the glycoprotein that is present on the surface of cells derived from epithelial carcinomas but not on cells of normal ovarian tissues (4). Some normal non-ovarian tissues, including endometrium, contain relatively small amounts of CA-125 (5).

A monoclonal antibody-based assay for CA-125 in serum is available commercially for investigational purposes. In one study of over 800 healthy controls (3), more than 98%

had concentrations of CA-125 in serum of <35 kU/L, and more than 99% had concentrations of <65 kU/L. In contrast 82% of 101 patients with ovarian cancer had serum CA-125 values exceeding 35 kU/L, and 74% of these patients had values >65 kU/L (3). In addition to increased CA-125 in a large percentage of ovarian-cancer patients, CA-125 value correlated significantly with changes in the disease during treatment and during recurrence (1).

For one to interpret CA-125 results properly, knowledge of conditions other than ovarian cancer that affect serum CA-125 concentrations is important. Non-malignant disease states such as cirrhosis of the liver reportedly cause increases in CA-125 to >400 kU/L (2). CA-125 is also increased in some subjects during the first and second trimesters of normal pregnancy, although values did not exceed 140 kU/L (6).

In this report, we describe a healthy subject in whom there were extreme increases in CA-125 in serum in association with her menstrual period.

### Methods

**CA-125 assay.** The immunoradiometric assay kits for CA-125 were provided by Abbott Laboratories' Diagnostic Division. Manufacturer's instructions (7) were followed, except that all the assays were done in singlet instead of duplicate. In our laboratory, the intra-run precision (CV) of the assay was 9.5% for 10 control runs, which had a mean value of 104 kU/L.

**Subjects.** Thirty-nine healthy women, all volunteers, were recruited from the Floyd Memorial Hospital staff. They ranged in age from 23 to 60 years. Over 90% were premenopausal. The five subjects who were included in the study of CA-125 values during the menstrual cycle were 24 to 45 years old. Below, we give a description and pertinent medical history of the subject, T. L., whose CA-125 values were grossly increased.

### Results

The normal reference interval for CA-125 in our population of 39 women was from <6.5 to 51 kU/L. During this normal-range study, subject T. L. showed a pronounced increase in CA-125. Subsequent evaluation demonstrated that this increase was associated with her menstrual period (Figure 1). Immediately before the menstrual period, the values for serum CA-125 in this subject were within the normal reference interval, 0 to 35 kU/L, established in large clinical studies by others (3) and confirmed in our labora-

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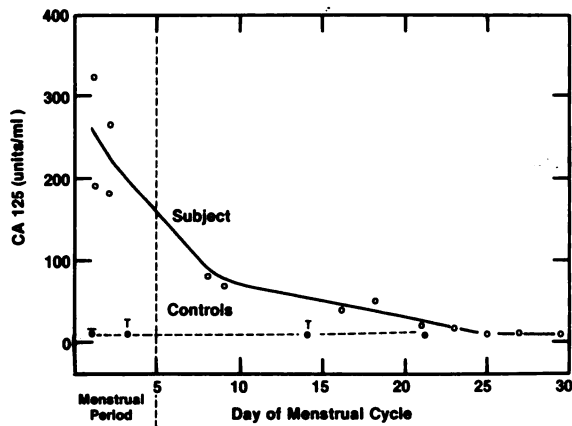


Fig. 1. CA-125 concentrations in serum of the subject, T. L. (open circles) and controls (closed circles)

Bars indicate the range of CA-125 values for four or five individuals. Data for T. L. are from samples collected during five menstrual cycles

tory. But, within one day after the onset of the menstrual period, the serum CA-125 concentration in T. L. increased by 10- to 20-fold, >300 kU/L. Five other healthy subjects had no pronounced variation in serum CA-125 during their menstrual cycles. After the initial increase at the onset of menstruation, values for CA-125 in T. L. subsequently decreased steadily during the remainder of the cycle.

Assuming that the substantial majority of CA-125 influx into the systemic circulation is confined to the first two days of the menstrual cycle, we calculated an apparent biological half-life for CA-125 in the circulation to be 6.3 days with use of all data points. The half-life was 6.4 days calculated on the basis of data from a single menstrual cycle.

Subject T. L., age 44, was evaluated by clinical gynecological examination, pelvic ultrasound, and computed tomography scans within two weeks after the initial discovery of increased CA-125. At that time, she had some history of menstrual pain and heavy menstrual flow. The examination revealed an enlarged uterus, possible fibroids, and a slight thickening of the myometrium, but no evidence of malignancy or endometriosis. The results of a repeat clinical examination eight months later were the same.

## Discussion

Although several non-malignant conditions can result in increased CA-125, there are no reports of CA-125 values greater than 200 kU/L in a healthy subject. In a study of 888 healthy blood donors (3), the highest CA-125 value was 161 kU/L. In another report (6), only 3% of 386 non-pregnant patients who had various non-malignant gynecological disorders had serum CA-125 values >65 kU/L. In four of seven of the gynecological patients in this report who had an initially increased value for CA-125, the second sample was normal. The authors considered this to be a non-repeatable false-positive result. However, fluctuations during the menstrual cycle such as we described here might account for the inconsistency in these cases.

The mechanism for the rapid and pronounced increase in CA-125 at the onset of menstruation that we observed here is unknown. Dr. Robert Bast has suggested tubal reflux as a possible cause (personal communication). According to this hypothesis, a portion of endometrial tissue, which contains CA-125 (5), is refluxed into the peritoneal cavity via the fallopian tubes and degraded rapidly, and the CA-125 so released is absorbed into the systemic circulation. This explanation is consistent with our observations. Takahashi

et al. (8) found increased CA-125 in seven of eight patients with adenomyosis. The enlarged uterus and slight thickening of the myometrium in T. L. raises the possibility of adenomyosis. However, she has been asymptomatic and has no progressive clinical indications of adenomyosis. In the absence of definitive surgical evidence, the possibility nevertheless exists that adenomyosis contributed to the increased CA-125 in this subject.

Half-life data for CA-125 in the circulation may be used to estimate the time required for this marker to decline to within normal limits after surgical excision of an ovarian tumor. The half-life for CA-125 for the subject in this report was 6.4 days, a value in reasonable agreement with the half-life of 4.8 days reported by Canney et al. (9), using data from a patient who had complete surgical removal of the tumor.

Our findings demonstrate that serum CA-125 concentrations can fluctuate pronouncedly during the menstrual cycle. The significance of these findings to the monitoring of CA-125 in pre-menopausal women depends on the prevalence of this fluctuation in the general population. In a Japanese study (10), six of 30 menstruating women were found to have CA-125 concentrations greater than 65 kU/L, but none had values exceeding 100 kU/L during their menstrual periods. Clearly, more extensive population studies are needed. In the meantime, abnormally high baseline or pre-treatment results for CA-125 in pre-menopausal women should be interpreted with caution—and the results should be confirmed at different stages of the menstrual cycle.

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