SERUM CA 125 LEVELS BEFORE, DURING, AFTER TREATMENT FOR ENDOMETRIOSIS

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SUMMARY

The levels of CA 125 in the serum was evaluated in 66 patients with endometriosis diagnosed and staged according to the revised American Fertility Society (AFS) classification via laparoscopy. The patients received a 6 month course of gonadotropin-releasing hormone (GnRH) agonist. Serum CA 125 levels were measured before, during (3 months and 6 months after the initiation of therapy) and 6 months after cessation of the medication. Patients with minimal and mild endometriosis had mean pre-treatment values significantly higher than control subjects in the luteal phase of the cycle or postmenopausal women ($p<0.05$) but the overall mean value was still below 35 U/ml. In contrast 80.7% of patients with moderate or severe endometriosis had levels in excess of 35 U/ml and the mean values for these groups were significantly elevated ($p<0.005$). Levels of CA 125 fell to those found in normal controls, during treatment, but rose again following cessation of the treatment. Nine of 19 subjects whose follow-up values of CA 125 exceeded 35 U/ml had a proven recurrence of endometriosis, while only 3 of 47 patients with values less than 35 U/ml had laparoscopically proven persistance or recurrence. The sensitivity and spesificity of CA 125 were 75% and 83.3% respectively and positive predictive value (PPV) was 46.36% as a predictor value of the recurrence.

The data suggest that CA 125 levels may be a reliable indicator for monitoring the efficacy of GnRH agonist treatment of endometriosis, but its predictor value of recurrence is low.

Key Words : Serum CA 125, endometriosis, gonadotropin-releasing hormone agonists.

INTRODUCTION

CA125 is a high molecular-weight glycoprotein that is expressed on the cell surface of some derivates of embryonic coelomic epithelium (1, 2). In adults, immunocytochemical techniques have demonstrated the presence of CA 125 on the epithelium of the fallopian tubes, endometrium, and endocervix and on the peritoneum, pleura and pericardium (1,2). High concentrations of CA 125 have been demonstrated in a variety of normal biological fluids such as cervical mucus, human milk, saliva and amniotic and peritoneal fluids (3-7). Bast et al. reported that 82% of patients with ovarian carcinoma, but only <1% of apparently healthy controls, have elevated peripheral blood levels of CA 125 (8). Milder elevations have been demonstrated in patients with several benign gynecological conditions, such as acute pelvic inflammatory disease (PID), adenomyosis (9) during mensturation and early pregnancy (10, 11). Since Barbieri et al. (12) demonstrated elevated serum concentrations of CA 125 in patients with advanced endometriosis, various investigators (7, 13, 14) have attempted to use this antigen in the preoperative diagnosis of endometriosis. If this antigen is specific for entometriosis, serum levels should decrease as endometriosis responds to gonatodropin-releasing hormone (GnRH) agonist treatment.

The present study is a prospective assessment of GnRH agonist treatment of endometriosis in term of the change in the extent of the disease and in relation to the change in CA 125 levels and also in the follow up period for detection of the recurrence.

MATERIALS AND METHOD

Sixty six patients with endometriosis diagnosed via laparoscopy and staged according to the revised American Fertility Society (AFS) classification were studied. Twenty of them were minimal, 20 mild, 15 moderate and 11 were severe endometriosis. Their ages varied between 18-41 years. They were all infertility patients with a duration of infertility ranging from 2 years to 9 years. They were treated with the GnRH agonist Buserelin (Dser(+Bu)^6-Pro-NET LHRH) 200 μgr/6h intranasally for 6 months. At the end of 6 months of therapy all patients underwent a second look laparoscopy in order to determine the therapeutic response and restaging.

The serum CA 125 levels were analysed in all patients in the luteal phase before starting the treatment, in the third and sixth months during the treatment and in the sixth month after the cessation of the treatment. The levels of CA 125 have been measured in 20 regular menstruating women with a normal pelvis at laparoscopy during luteal phase and in 20 post menopausal women who were not on hormone replacement therapy and with no history of post-menopausal bleeding, endometrial and ovarian carcinoma for comparison.

Commercially available immunoradiometric assay (IRMA) kits were used for the determination of CA 125 (Sorin, Biomedica, Sallugia, Italy). The working range of this assay was 7.2 to 500 U/ml. In different groups, mean ± standard deviation were calculated, and for statistical comparison, student's t-test and Chi-square test were used.

RESULTS

The serum levels of CA 125 in two groups of normal controls and pretreatment values in all the endometriosis patients grouped by AFS classification are shown in Table I.

None of the 20 post menopausal patients and only 2 of 20 normal regularly menstruating women had serum CA 125 in excess of 35 U/ml. The values of serum CA 125 in patients with minimal and mild endometriosis were not significantly different from each other but were significantly higher ($p<0.05$) than those of combined control group. Thirty percent of these patients had serum CA 125 levels higher than 35 U/ml.

The patients with moderate and severe endometriosis had serum CA 125 levels significantly greater than the levels of the patients with minimal and mild disease ($p<0.05$) and controls ($p<0.005$). 80.7 % of these patients had values greater than 35 U/ml.

In Table II the changes in serum CA 125 levels of the patients with endometriosis at the third month and sixth month of treatment and at the sixth month of post treatment are shown.

A significant decrease in mean serum CA 125 values was seen in all groups by the third month of the treatment ($p<0.02$) and this was maintained until the end of the treatment (6 months) but with no further decrease. After the treatment was stopped there was an increase in the mean serum CA 125 values but these changes were not significantly different from the treatment values in minimal and mild groups.

Nine of 19 patients whose follow up values of serum CA 125 exceeded 35 U/ml, recurrence of endometriosis was confirmed by further laparoscopic assessment, on the other hand 3 of 47 patients with values of serum CA 125 less than 35 U/ml have developed recurrence during follow-up to date. The sensitivity and spesificity of CA 125 were 75% and 83.3% respectively and PPV was 46.36% as a predictor of the recurrence. All patients who developed recurrence after the cessation of the treatment were in moderete or severe endometriosis group.

Table I: Serum CA 125 levels in luteal phase of normal menstruating women, post menopausal women and patients with endometriosis clasified by the revised American Fertility Society classification.

	Ca 125 U/ml		
	No patients	Mean±SD	Range
Regular menstruating women	20	17.4±2.3	10.2-37.4
Post menopausal women	20	11.2±1.9	6.7-18
Minimal endometriosis	20	26.4±4.7	8-124
Mild endometriosis	20	29.7±6.8	9.5-172
Moderate endometriosis	15	89.4±37.5	10-287
Severe endometriosis	11	96.2±43.5	18-275

Table II: The serum CA 125 levels of the patients with endometriosis before treatment, at the third and sixth month of the treatment and six months post treatment.

	Ca 125 U/ml (Mean±SD)			
	Pre treatment	3rd month of treatment	6th month of treatment	6 months post treatment
Minimal endometriosis	26.4±4.7	14.7±4.3	14.2±4.1	21.3±4.2
Mild endometriosis	29.7±6.8	16.4±5.2	15.7±5.6	24.6±7.8
Moderate endometriosis	89.4±37.5	22.4±9.6	18.2±4.3	34.7±24.6
Severe endometriosis	96.2±43.5	25.7±12.6	23.4±14.7	81.4±36.7

DISCUSSION

This study has assessed the value of CA 125 as a marker of clinical progress in the treatment of endometriosis with a GnRH agonist buserelin. These peptides induce a state of "medical castration" and subsequent hypo-estrogenism will cause regression of estrogen dependent implants.

Non invasive diagnostic methods for evaluation of treatment and for the detection of recurrence are currently being sought (16, 17). Using CA 125 as a marker for endometriosis we found as did others (13, 14) that significantly elevated levels of CA 125 in serum became more evident only in advanced stages of the disease (Stage III and IV). In stage I and II endometriosis the serum levels of CA 125 are low, precluding its measurment as a diagnostic test of disease. Nevertheless, the serum test seems to be useful in monitoring patients during and after medical therapy, because a significant correlation between CA 125 levels and the clinical course of the disease was observed (18).

This study indicates that measurement of serum CA 125 levels has value in identifiying the cases most likely to have advanced endometriosis. Serial measurements during therapy relate to extend of inactivation of endometriotic implants and return to abnormal values after therapy predicts reactivation or persistance of endometriosis.

Twenty-one of 26 women with moderate or severe endometriosis had elevated pre-treatment levels of CA 125 in excess of 35 U/ml. Levels fell to the levels of those found in normal controls during treatment but rose again following cessation of treatment in 19 women. Nine of this 19 subjects had a proven recurrence of endometriosis. Only 3 of 47 patients with values less than 35 U/ml had laparoscopically proven recurrence.

The decrease in serum CA 125 levels in patients with endometriosis treated with GnRH agonist probably occurs because of inhibition of endometrial growth and endometrial activity from both normal and ectopic endometrial tissues. During follow-up, increase in CA 125 values above 35 U/ml were more likely to indicate reactivation of endometriosis than when no increase were observed. On the other hand, Franssen et al. found the decreasing effect of suppressed ovarian activity on serum CA 125 concentrations and the rebounding of CA 125 concentrations after cessation of therapy going parallel with the restoration of ovarian activity, could have been expected (19). It may explain why we have found only nine of 19 subjects whose follow-up values of CA 125 exceeded 35 U/ml had a proven reccurence of endometriosis after 6 months cessation of treatment.

The patients with endometriosis is often subjected to repeated laparoscopic examination of the pelvis to assess progress during and after therapy or to determine whether recurrence of disease has occured. We suggest that CA 125 is a valuable adjuvant in the management of endometriosis when it is treated with GnRH agonist. Surgical intervention may be avoided and medical therapy adjusted according to the CA 125 levels and relapse or remission may be diagnosed in selected patients, especially physcologically depressed because of long duration therapy and repeated surgical procedures. The initial assessment of women with suspected endometriosis should include laparoscopy, biopsy and CA 125 measurements. In those patients who have elevated levels, CA 125 may be used to monitor progress when GnRH agonist treatment is used.

Once these levels have been normalized definitive surgery or cessation of therapy may be contempted and CA 125 levels may be used for future follow-up.

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