Serum CA 125 concentrations in women with endometriosis or uterine fibroids treated with gonadotrophin-releasing hormone agonist analogues

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Abstract **We assessed the possible role of CA 125 in the monitoring of gonadotrophin-releasing hormone (GnRH) agonist analogue therapy in women with endometriosis and uterine fibroids. Serum concentrations of this cell surface antigen did not correlate with uterine volume and appeared to have no value in the assessment of shrinkage of uterine fibroids during GnRH agonist treatment. While CA 125 levels were not always elevated in subjects with endometriosis, they fell during treatment in all patients. The change accurately reflected therapeutic progress in these women and was of particular value in those patients who had commenced therapy with elevated levels. It is suggested that CA 125 may be useful in the monitoring of therapeutic progress in selected patients with endometriosis treated with GnRH agonists; the need for surgical follow-up may be obviated.**

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CA 125 is a cell surface antigen, associated with a high-molecular-weight glycoprotein, which is recognised by the murine monoclonal antibody, OC 125. Bast *et al.*[1,2] first described the radio-immunoassay and demonstrated elevated levels of CA 125 (> 35 U/ml) in the sera of 82% of 101 women with non-mucinous epithelial carcinoma of the ovary and 1% of an apparently healthy group of 888 blood donors. Elevated levels of CA 125 have since been described in a number of malignant and benign diseases as well as certain physiological conditions such as menstruation and early pregnancy.[3]

Several studies have noted significant elevation of CA 125 levels in women with endometriosis, uterine fibroids and other benign gynaecological conditions and suggested that this antigen may be of value, both in the diagnosis of the disease and the monitoring of therapy.[4,5] The availability of a marker of disease which could be used to monitor therapeutic progress is of considerable value, since it might avoid expensive and invasive follow-up investigations. We treated women who had proven endometriosis or uterine fibroids with gonadotrophin-releasing hormone (GnRH) agonist analogues and attempted to determine the value of CA 125 in their therapeutic response to these peptides.

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Subjects and methods

Patients

Endometriosis

Eight women with confirmed endometriosis were treated with a GnRH agonist analogue (DTrp^6, Pro^9 *N*-ethylamide LHRH) in a daily dose of 200 µg. Treatment was initiated during the follicular phase of the cycle. Blood was taken for the measurement of serum CA 125 concentrations before the commencement of therapy, after 8 - 12 weeks' treatment and before surgery at the conclusion of treatment (16 - 24 weeks). Seven of the 8 women had objective reassessment of their endometriotic deposits; the 8th declined further surgery and was reassessed symptomatically.

Uterine fibroids

Eleven women with fibroids were treated with a long-acting analogue, 3,6 mg Zoladex (D-Ser (Bu^t)^6 Azgly^{10}-LHRH; ICI Pharmaceuticals), administered as a depot implant at 4-weekly intervals for 20 - 24 weeks. Treatment was started in the follicular phase of the cycle and myomectomy was performed within 4 weeks of the last implant. Blood was taken for CA 125 measurements at the commencement of therapy, after 12 and 20 weeks of treatment and 8 weeks after the last depot injection (6 - 8 weeks after myomectomy). Uterine volume was determined by means of ultrasound on each of these occasions.

Control subjects

Ten healthy volunteers with normal ovulatory cycles had serum CA 125 levels determined on day 6 of the cycle. These measurements served as normal control values for this study.

CA 125 assay

CA 125 was measured by means of a simultaneous sandwich solid-phase radio-immunoassay with a commercial kit (Abbott CA 125 RIA, Abbott Laboratories Diagnostic Division, North Chicago, Ill.). The sensitivity of the assay was 5 U/ml and the intra-assay coefficient of variation was 10%. All samples described here were measured in a single assay.

Statistics

Analysis of variance was used to determine differences between groups in CA 125 levels. Where necessary, because of the non-homogeneity of variance, a log transformation of the CA 125 levels was made.

Consent

Consent to perform these studies was obtained from the Ethics and Research Committee of the University of Cape Town Medical School. All subjects studied gave written informed consent.

Results

CA 125 concentrations at the initiation of therapy

The serum concentrations of CA 125 in the control subjects and the two groups of patients are shown in Fig. 1. There was a significant difference in the initial levels of CA 125 in the 3 groups ($F_{2,26} = 4{,}338$; $P < 0{,}025$).

The mean concentration (± SEM) of CA 125 in the patients with endometriosis was 65,9 ± 24,7 U/ml with a range of 8,3 - 200,9 U/ml. This was significantly higher than the levels found in the control subjects which ranged from 5,8 to 38,3 U/ml ($F_{1,26} = 6{,}178$; $P < 0{,}025$). In contrast, in the women with uterine fibroids, the initial CA 125 concentrations were not significantly different from those of the controls and ranged from 3,5 to 45,8 U/ml with a mean (± SEM) of 19,2 ± 4,3 U/ml. Although the mean value and the range of CA 125 were significantly higher in the women with endometriosis, there was considerable overlap in the three groups (Fig. 1).

CA 125 concentrations during therapy in endometriosis patients

All 8 patients with endometriosis demonstrated clinical improvement during treatment. Serum oestradiol concentrations fell to < 200 pmol/l within 3 weeks of commencing agonist treatment and were maintained at this level throughout therapy. Six of the women underwent tubal surgery at the conclusion of therapy and at laparotomy there was no evidence of active endometriosis. One woman had an umbilical endometrioma which regressed during treatment; she has subsequently remained asymptomatic. The remaining patient stopped therapy after 6 months and remains symptom-free 2 years later.

In Fig. 2 the changes in CA 125 concentrations during treatment are illustrated. CA 125 concentrations fell in all patients. The mean concentration pre-treatment (65,9 ± 24,7 U/ml) fell to 12,3 ± 4,7 U/ml after 8 - 12 weeks and finally reached a level of 6,9 ± 1,24 U/ml at the conclusion of therapy ($F_{2,21} = 15{,}855$; $P < 0{,}001$).

There was a significant change between the initial measurements and those taken after 8 - 12 weeks' treatment ($F_{1,21} = 24{,}735$; $P < 0{,}001$) and at the end of therapy ($F_{1,21} = 22{,}791$; $P < 0{,}001$). However, the fall between 8 - 12 weeks and the end of treatment was not significant, suggesting that the maximal therapeutic benefit was achieved in the first 3 months of the induced hypo-oestrogen state.

In Fig. 3 the changes in CA 125 concentrations in one of the patients with severe endometriosis are noted. This woman presented with ascites and a pelvic mass, and at exploratory laparotomy, severe endometriosis was diagnosed and histologically confirmed. Initial CA 125 levels were 137,1 U/ml when treatment with GnRH agonist was instituted. CA 125 concentrations fell during the first 4 weeks of therapy and the patient improved clinically. The CA 125 levels subsequently reached a plateau suggesting therapeutic non-compliance, there was a rise in oestradiol concentrations and a relapse in her condition. She complained of abdominal and chest pain during menses and on examination, was found to have a right-sided haemothorax. Thoracotomy was performed and the tentative diagnosis of a pleural endometrioma was made — although the histological findings were not conclusive. GnRH agonist therapy was recommenced and CA 125 levels fell to 13,1 U/ml. At repeat laparotomy (to repair an incisional hernia) she was found to be free of active endometriosis. Throughout her treatment, the CA 125 concentrations accurately mirrored the endometriotic activity.

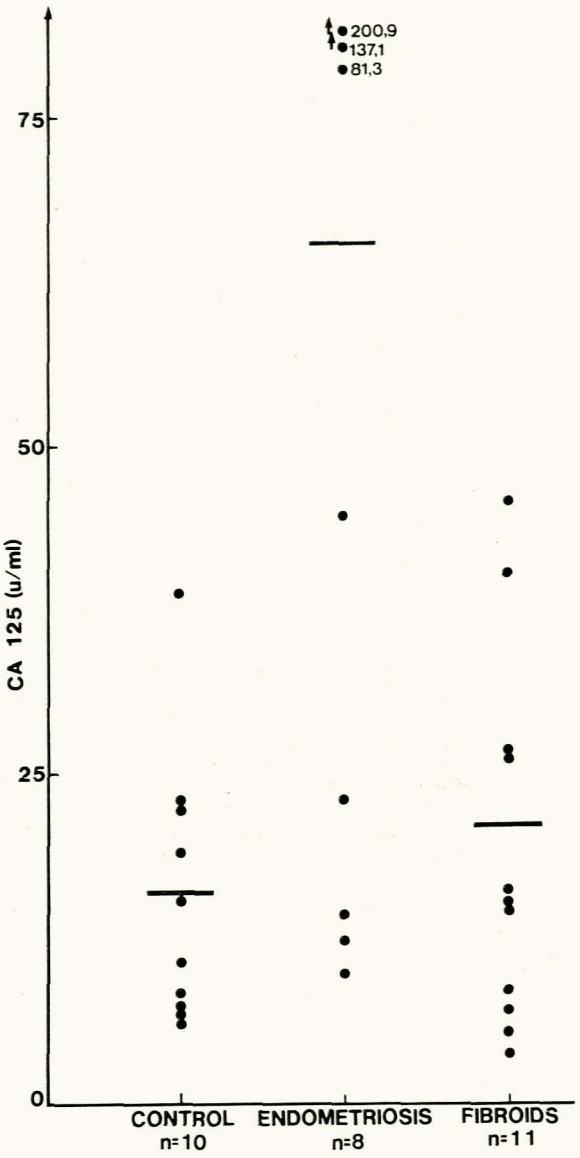

FIG. 1.
Serum concentrations of CA 125 in healthy women, women with endometriosis and women with uterine fibroids. The horizontal line indicates the mean of the values in each group. All samples were taken in the follicular phase of the ovarian cycle before therapy started. Although the mean value and the range of CA 125 levels were significantly higher in the women with endometriosis, there was considerable overlap in the three groups. Four of the subjects with endometriosis and 2 of the women with fibroids had initial values outside the normal range.

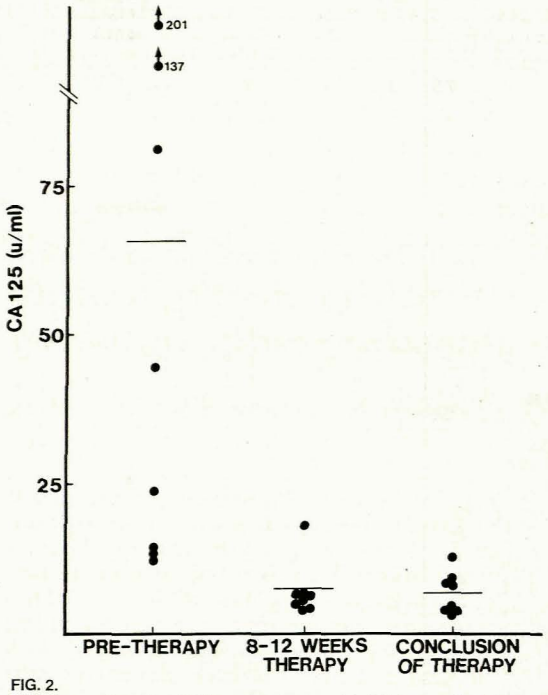

FIG. 2.
Changes in CA 125 levels during GnRH agonist therapy in 8 women with endometriosis. The horizontal bar shows the mean concentrations pre-treatment, after 8 - 12 weeks and at the end of therapy. There is a significant fall after 8 - 12 weeks of treatment and no further reduction in the next 12 weeks.

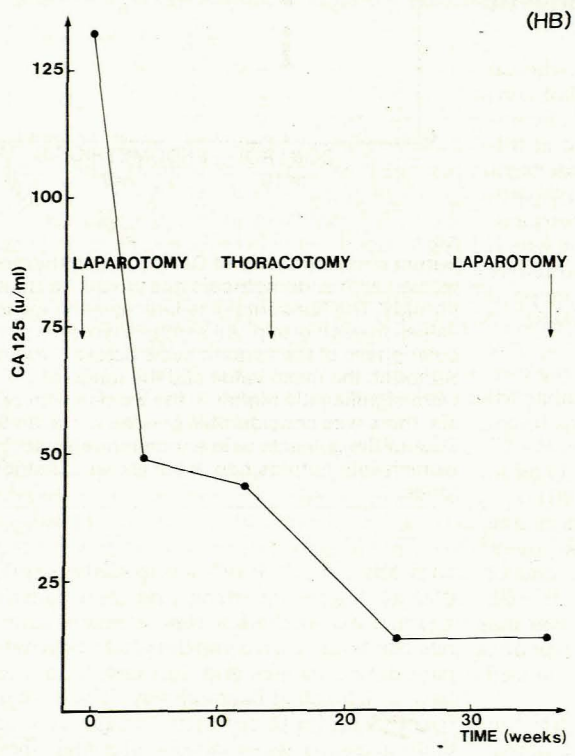

FIG. 3.
Response to GnRH agonist therapy in a patient with endometriosis. Her clinical course is described in the text. The times of surgical intervention are indicated by the arrows and the serum CA 125 levels accurately reflect her clinical course and symptomatology.

CA 125 concentrations in women with uterine fibroids

All 11 women treated with GnRH agonist analogue demonstrated a decrease in uterine and fibroid volume after 8 - 12 weeks of therapy. The uterine volumes and CA 125 levels pre- and post-therapy are given in Table I. There was no correlation between the volume of the uteri and CA 125 concentrations either pre-treatment or post-therapy and myomectomy (r = 0,364; T = 1,173; df = 9; P = 0,271 v. r = 0,576; T = 2,117; df = 9; P = 0,063). The CA 125 concentrations are illustrated in Fig. 4 and did not change significantly during therapy ($F_{3,40}$ = 0,056; NS).

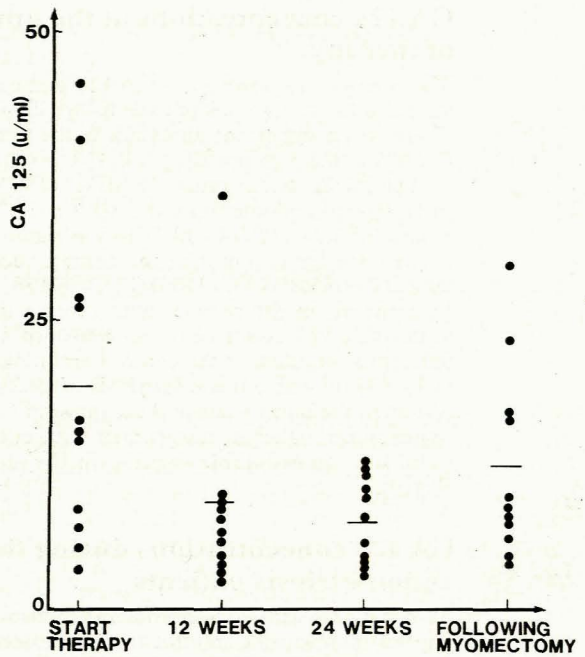

FIG. 4.
CA 125 concentrations in 11 women with uterine fibroids. Serum concentrations of CA 125 before therapy, after 12 and 24 weeks and after myomectomy and the recovery of the hypothalamic-pituitary-ovarian axis from GnRH agonist suppression are shown. The horizontal bar indicates the mean concentration at each of the times noted. Only 2 subjects had values outside the normal range before therapy and these values were not markedly elevated.

Discussion

This study has assessed the value of CA 125 as a marker of clinical progress in the treatment of endometriosis and uterine fibroids with GnRH agonist analogues. These peptides induce a state of 'medical castration' and the subsequent hypo-oestrogenism will cause regression of oestrogen-dependent conditions such as endometriosis and uterine fibroids.

It has been suggested that CA 125 is a marker of uterine fibroids and might be used to assess progress of patients treated with GnRH agonists.[6] However, in the patients presented here who were treated with GnRH agonists before myomectomy, CA 125 did not correlate with the size of the fibroids, the uterine volume or the response to therapy. The shrinkage of fibroids with GnRH agonist is best monitored by means of ultrasound, which has the added advantage of being able to describe the number, position and size of the fibroids. The small non-significant fall in CA 125 values which was demonstrated in the women with fibroids was

TABLE I.
Uterine volumes and CA 125 concentrations in women with fibroids treated with GnRH agonist analogues

	Before commencing GnRH agonist therapy		Post-GnRH agonist therapy 6- 8 weeks after myomectomy	
Patient No.	Volume (ml)	CA 125 (U/ml)	Volume (ml)	CA 125 (U/ml)
1	1 774	26,4	454	16,4
2	516	27,0	282	29,6
3	710	7,0	162	6,5
4	482	3,5	45	3,9
5	684	16,6	47	9,1
6	734	5,3	114	4,0
7	769	15,2	95	7,6
8	223	8,1	79	7,2
9	274	15,3	88	16,5
10	1 061	40,8	180	23,2
11	636	45,8	86	8,6

probably the consequence of suppression of derivates of coelomic epithelium by the induction of a hypo-oestrogen state.

Four of the 8 women with endometriosis had elevated pre-treatment levels of CA 125. All 8 patients demonstrated a fall of CA 125 during therapy with GnRH agonist and normal levels were achieved after only 8 - 12 weeks of treatment. At re-assessment of 7 patients during surgery no evidence of active endometriosis was found. The patient whose clinical course is described in Fig. 3 was temporarily non-compliant and her retarded clinical progress was illustrated by the CA 125 plateau; normal levels were only achieved once effective therapy was re-instituted.

In this study CA 125 levels correctly reflected the clinical improvement in the 4 women who initially had elevated levels while in the remaining patients CA 125 was reduced by 50% following GnRH agonist treatment. In contrast, CA 125 has been reported to be of limited value in the assessment of clinical progress during the treatment of endometriosis with danazol or medroxyprogesterone acetate[7] and may even rise after progesterone administration.[8]

Since endometriotic lesions are of embryonic coelomic epithelial origin, CA 125 is likely to be a marker of endometriosis. If the endometriotic tissue sheds this antigen, the detection thereof in peripheral serum is limited by the blood supply or the presence of fibrosis surrounding endometriotic deposits. CA 125 has a low specificity and elevated levels have also been reported in women with malignant ovarian tumours, pelvic inflammatory disease, endometriosis and other benign and malignant disease.[2,4,5] While CA 125 appears helpful in the follow-up of advanced ovarian malignant disease and the detection of recurrence, it is of limited value in the early diagnosis of, or as a screening test for epithelial carcinomas, since a minimum tumour load is required before CA 125 levels are elevated.[9-11]

With 35 U/ml as the upper limit of normal, elevated levels of CA 125 were reported by Barbieri *et al.*[12] in 54% of women with stage III or IV endometriosis, 14% of women with fibroids and 13% of women with stage II endometriosis. Similar results have been reported by other authors, but the low sensitivity of the measurement of CA 125 in endometriosis makes it an unsuitable screening test for this condition.[5,13]

The patient with endometriosis, however, 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 occurred. We suggest that CA 125 is a valuable adjuvant in the management of endometriosis when it is treated with GnRH agonist analogues. 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. The initial assessment of women with suspected endometriosis should include laparoscopy and biopsy and the measurement of CA 125. In those patients who have elevated levels, CA 125 may be used to monitor progress when GnRH agonist treatment is used, although its value with other forms of therapy is limited. Once these levels have been normalised, definitive surgery or cessation of therapy may be contemplated and CA 125 levels may be used for future follow-up.

While CA 125 is apparently of no clinical value in the monitoring of the response of fibroids to GnRH agonist treatment, it certainly has a role in the management of endometriosis. Repeated measurements of CA 125 in selected patients with endometriosis, in conjunction with clinical assessment, would be both cost-effective and less invasive than repeated surgical procedures.

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REFERENCES

1. Bast RC jun, Feeney M, Lazarus H, Nadler LM, Colvin RM, Knapp RC. Reactivity of a monoclonal antibody with human ovarian carcinoma. *J Clin Invest* 1981; **68:** 1331-1337.
2. Bast RC jun, Klug TL, St John E, *et al.* A radio-immunoassay using a monoclonal antibody to monitor the cause of epithelial ovarian cancer. *N Engl J Med* 1983; **390:** 883-887.
3. Jacobs I, Bast RC jun. The CA 125 tumour associated antigen: a review of the literature. *Hum Reprod* 1989; **4:** 1-12.
4. Pittaway DE, Fayez JA. The use of CA 125 in the diagnosis and management of endometriosis. *Fertil Steril* 1986; **46:** 790-795.
5. Niloff JM, Knapp RC, Schaetzl E, Reynolds C, Bast RC jun. CA 125 antigen levels in obstetric and gynecologic patients. *Obstet Gynaecol* 1984; **64:** 703-707.
6. Yamamoto T, Tomioka M, Urabe M, *et al.* The reduction of uterine leiomyoma by administration of intranasal luteinizing releasing hormone analogue (Buserelin) — the therapeutic experience for 16 patients (Abstract 03-22-124). Paper presented at the 8th International Congress of Endocrinology, Kyoto, Japan, July 17-23, 1988 (published by the International Society of Endocrinology in the preliminary programme, p. 151).
7. Kauppila A, Telimaa S, Rönnberg L, Vuori J. Placebo-controlled study on serum concentrations of CA 125 before and after treatment of endometriosis with danazol or high-dose medroxyprogesterone acetate alone or after surgery. *Fertil Steril* 1988; **49:** 37-41.
8. Ozasa H, Noda Y, Mori T. Progesterone increases CA 125 in endometriosis. *Fertil Steril* 1987; **47:** 699-701.
9. Lambert J. The value of CA 125 serum assay in the management of ovarian cancer. *Br J Obstet Gynaecol* 1987; **94:** 193-195.
10. Einhorn N, Bast RC jun, Knapp RC, Tjernberg B, Zurawski VR. Pre-operative evaluation of serum CA 125 levels in patients with primary epithelial ovarian cancer. *Obstet Gynecol* 1986; **67:** 414-416.
11. Schilthuis MS, Aalders JG, Bouma J, *et al.* Serum CA 125 levels in epithelial ovarian cancer: relation with findings at second-look operations and their role in the detection of tumour recurrence. *Br J Obstet Gynaecol* 1987; **94:** 202-220.
12. Barbieri RL, Niloff JM, Bast RC jun, Schaetzl E, Kistner RW, Knapp RC. Elevated serum concentrations of CA 125 in patients with advanced endometriosis. *Fertil Steril* 1986; **45:** 630-634.
13. Guidice LC, Jacobs A, Pineda J, Bell CE, Lippmann L. Serum levels of CA 125 in patients with endometriosis: a preliminary report. *Fertil Steril* 1986; **45:** 876-878.