

Serum CA 125 levels and spontaneous abortion

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OBJECTIVE: Previous reports have suggested that serum CA 125 levels in patients who spontaneously abort in the first trimester of pregnancy differ from the levels of patients who successfully complete their pregnancies. Low CA 125 levels have been suggested to predict spontaneous abortion, although an increased rate of first-trimester spontaneous abortion has also been reported in women with elevated CA 125 levels early in pregnancy. The purpose of this study was to prospectively compare serum CA 125 levels of women who abort in the first trimester with levels of those women whose pregnancies progress beyond 12 gestational weeks.

STUDY DESIGN: A total of 188 pregnant patients had weekly serum CA 125 levels obtained after a prepregnancy baseline value was determined. Levels of the antigen in women who ultimately had a first-trimester spontaneous abortion were compared with CA 125 levels from women whose pregnancies continued past the first trimester.

RESULTS: There was no statistically significant difference in the CA 125 levels of patients who aborted compared with those of women whose pregnancies continued. In addition, among patients with CA 125 values > 150 U/ml there was also no statistically significant difference in the proportion of patients who aborted compared with controls.

CONCLUSION: Serum CA 125 levels are not predictive of spontaneous abortion in the first trimester of pregnancy. (AM J OBSTET GYNECOL 1995;172:695-9.)

Key words: CA 125, spontaneous abortion, pregnancy

OC 125 is a monoclonal antibody obtained by somatic hybridization of β -lymphocytes from mice immunized with cells from an ovarian carcinoma cell line. Its antigenic determinant, CA 125, is associated with a high molecular weight glycoprotein expressed as derivatives of coelomic epithelium.¹⁻³ During early pregnancy CA 125 levels are increased, peaking by 10 gestational weeks before declining in the late first trimester.⁴⁻⁷ Check et al.⁸ reported that high levels of CA 125 in the serum of pregnant patients at 18 to 22 days and 6 weeks after conception were correlated with eventual spontaneous abortion. Furthermore, they found that CA 125 levels >150 U/ml were predictive of eventual spontaneous abortion, even after viability by ultrasonography had been established. In addition, very high levels of CA 125 in the first trimester have been associated with fetal chromosomal abnormalities.⁹ Brumstead et al.¹⁰ noted a ten-

dency toward lower levels of CA 125 in patients with spontaneous abortions; however, their findings did not reach statistical significance. Similarly, a lower mean serum CA 125 at 4 to 8 weeks' gestation has been observed in patients who aborted, compared with the level of those with a successful pregnancy outcome.¹¹ Finally, Witt et al.¹² noted lower serum CA 125 values in asymptomatic pregnant patients who ultimately miscarried and observed higher levels of the antigen in the serum of symptomatic patients who aborted.

The loss of an early pregnancy can be devastating to an infertile couple. A simple serum value, which would aid assessing the prognosis for the well-being of the pregnancy, would offer considerable benefit in counseling patients. Therefore, to clarify the relationship between serum CA 125 levels and spontaneous abortion, this study was undertaken with two objectives: first, to prospectively determine and compare serum CA 125 levels at weekly intervals in women who ultimately have a spontaneous abortion with levels of the antigen in women whose pregnancies progress beyond the first trimester, and second, to specifically determine if the previously suggested CA 125 value of 150 U/ml is useful in distinguishing successful from unsuccessful pregnancies during the first trimester.

Material and methods

A total of 567 patients attempting conception were prospectively recruited from the Fertility and Endo-

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Table I. Demographic data

	Group I, patients with spontaneous abortion (n = 66)	Group II, patients without spontaneous abortion (n = 122)
Age (yr)	32.5 ± 0.4	32.5 ± 0.4
Gravidity	1.6 ± 0.2	1.4 ± 0.1
No. of previous miscarriages	1.0 ± 0.2	0.9 ± 0.1
No. of live births	0.3 ± 0.0	0.2 ± 0.1
Diagnosis of endometriosis (No., %)	8 (12%)	23 (19%)
In vitro fertilization/gamete intrafallopian transfer (No., %)	7 (11%)	18 (15%)
Ethnic origin		
Asian	0 (0%)	3 (2.5%)
Black	2 (3.1%)	1 (0.8%)
White	62 (93.8%)	118 (96.7%)
Other	2 (3.1%)	0 (0%)

Data expressed as mean ± SEM.

crine Unit of the Brigham and Women's Hospital in Boston and from the Pennsylvania private practice of the Reproductive and Endocrine/ Infertility Service at Cooper Hospital University Medical Center, Camden, N.J. The study was approved by the appropriate Institutional Review Boards for the two study sites. All patients gave informed consent. Patients then had prepregnancy blood obtained for CA 125 determination during the nonmenstrual portion of the follicular phase of the menstrual cycle, and the CA 125 level was measured. Patients who conceived during the 2-year study period also had blood obtained for CA 125 levels during gestational weeks 4, 5, 6, 7, 8, and 12. The interval between prepregnancy and pregnancy blood drawings varied from 1 to 21 months. Gestational age was calculated from the last menstrual period. In stimulated cycles in which the day of conception was known with certainty this date was used and 14 days was added to arrive at the date of the last menstrual period. Each blood sample was immediately centrifuged and the aliquoted serum stored at -70° C for later analysis.

Of the 567 patients enrolled, 236 conceived during the study interval; 38 of these were lost to follow-up. Three women did not have subsequent CA 125 determinations, and seven had either an ectopic pregnancy or a voluntary termination of pregnancy. Thus, of the original 236 subjects, 188 patients remained for data analysis and were divided into two groups. Group I (n = 66) consisted of patients who experienced a spontaneous abortion during the first 12 weeks of pregnancy. Women who did not have spontaneous abortion during the first trimester (n = 122) comprised group II. Pregnancy outcome was determined by patient reporting, hospital records, and follow-up phone calls as necessary. CA 125 levels were determined by an immunoradiometric assay (Centacor, Malvern, Pa.) run in duplicate; results are expressed in arbitrary units on the basis of a primary reference standard. The interassay

and intraassay coefficients of variation were 11.5% and 9.5%, respectively.

Statistical analysis of the demographic data was performed with the Wilcoxon rank-sum test and Fisher's exact test as appropriate. Serum CA 125 levels in this population were not normally distributed. To account for this distribution, the data were natural-log transformed before statistical analysis. For clarity the non-log-transformed data are presented in the tables and figure. Transformation of the data did not alter the statistical analysis or the conclusions in any way. CA 125 values over time were compared within each group by repeated-measures analysis of variance blocked in groups of three by time to account for subject attrition. Pairwise comparisons for groups versus time among the means were performed by the Student-Neuman-Keuls test. The CA 125 values between groups over time were analyzed by two-way analysis of variance. Proportional CA 125 data were compared with Fisher's exact test or the χ^2 test with the Yates' correction as necessary. Results are reported as mean ± SEM. Statistical significance was assumed for $p < 0.05$. For power calculations $\alpha = 0.05$ and $\beta = 0.20$ were used.

Results

There were no statistically significant differences between the groups with respect to age, gravidity, number of previous spontaneous abortions, or number of previous live births. Similar proportions of subjects in each group had a condition known to be associated with elevated CA 125 levels (endometriosis or controlled ovarian hyperstimulation for assisted reproduction). The ethnic makeup of the two groups was also similar (Table I). Overall, 76% of the patients had infertility. There was no statistically significant difference between the groups in the proportion of subjects with subfertility resulting from ovulatory disorders (17.1% vs 11.5%), tubal factor (5.2% vs 4.9%), luteal-phase insufficiency

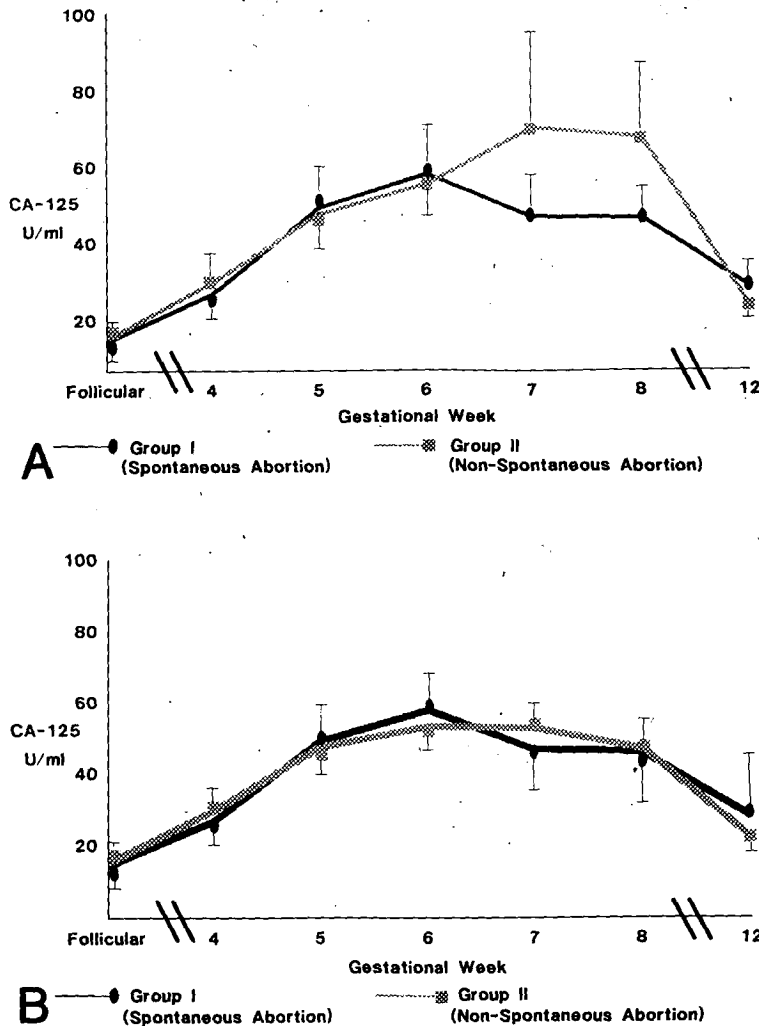


Fig. 1. Serum CA 125 levels by gestational week. A, All patients included. B, Excluding single outlier in group II.

(6.3% vs 4.9%), and male factor (7.3% vs 4.9%) for groups I and II, respectively. The majority of patients did not have a definite infertility diagnosis at study entry. A total of 27% of subjects had a history of recurrent abortion. There was no difference in the proportion of these individuals with respect to uterine factors (1.8% vs 0%), luteal-phase insufficiency (4.6% vs 1.9%), and immunologic causes (9.1% vs 3.8%) for groups I and II, respectively. As in the case for the infertility patients, the majority of patients with recurrent miscarriage lacked a definitive diagnosis at study entry.

The mean CA 125 level in women from group I rose from 14.4 ± 1.2 U/ml pre-pregnancy to a peak of 57.9 ± 15.4 U/ml at 6 gestational weeks. The difference over time did not reach statistical significance in this group (Fig. 1, A). Among group II subjects the mean CA 125 level increased from 15.1 ± 0.7 U/ml

preconception to a maximum of 70.1 ± 18.3 U/ml at 7 weeks' gestation. The values were different over time, with a statistically significant difference noted at weeks 7 and 8 of gestation compared with preconception baseline levels, $p < 0.05$. There was one significant outlier in group II. A single patient who did not abort had a markedly elevated CA 125 level, reaching a peak of 1060 U/ml at gestational week 7. When the data were reanalyzed excluding this patient, the two curves became virtually identical (Fig. 1, B). There was no statistically significant difference between the two groups over time. To answer the question whether there was a difference in CA 125 levels between those with a spontaneous abortion (group I) and those who did not abort (group II), a separate analysis was carried out comparing the CA 125 curves for the two study groups by week of spontaneous abortion. No statistically significant difference between the groups was found in those who

Table II. Distribution of CA 125 levels with a cutoff value of 150 U/ml

	No. of patients with CA 125 level >150 U/ml	No. of patients with CA 125 level ≤150 U/ml
Patients with spontaneous abortion	6 (33%)	60 (35%)
Patients without spontaneous abortion	12 (67%)	110 (65%)

Percentages in parentheses.

aborted at weeks 5, 6, 7, and 8. An insufficient number of patients with spontaneous abortions between weeks 9 and 12 did not permit analysis at the 12-week point. The power of the study for patients with spontaneous abortion was 0.95 at week 5, 0.99 at week 6, 0.85 at week 7, and 0.77 at week 8.

To test the hypothesis that a CA 125 level >150 U/ml in early gestation was predictive of eventual spontaneous abortion, particularly after normal results of an ultrasonographic examination, as previously reported,⁸ the proportion of patients with CA 125 levels >150 U/ml in the study groups was compared. There was no statistically significant difference between the groups in the proportion of patients with CA 125 levels >150 U/ml (Table II). Similarly, when analyzed by study week of gestation, there was again no statistically significant difference between the groups at weeks 6, 7, and 8. No patient in either group had a CA 125 level >150 U/ml at weeks 4, 5, or 12 of gestation or at pre-conception testing.

Further analysis of the patients with peak CA 125 levels >150 U/ml revealed that one of six group I patients had endometriosis, whereas one of 12 group II patients had this diagnosis (not significant). In addition, one group I subject and four group II patients with CA 125 levels >150 U/ml conceived by assisted reproduction. An additional two of the aborters and five of the nonaborters with higher CA 125 levels underwent ovulation induction. Thus there were two patients in both group I and group II with CA 125 levels >150 U/ml who had neither endometriosis nor underwent ovarian stimulation in the index cycle.

Comment

To date, the medical literature has been divided regarding the significance of serum CA 125 levels in women with spontaneous abortion. Early reports suggested that very high levels of the antigen CA 125 were associated with pregnancy loss and perhaps even with chromosomal abnormalities in the fetus.^{8,9} Check et al. found that CA 125 levels >150 U/ml were predictive of spontaneous abortion; however, that study was retrospective and did not attempt to follow up patients throughout early pregnancy to determine if differences in CA 125 levels in aborters and nonaborters might exist. Other investigators have reported both decreased and unchanged CA 125 levels in aborters compared

with controls.¹⁰⁻¹² This study was undertaken to prospectively follow up a large cohort of women in the first trimester of pregnancy to determine whether a difference in serum CA 125 obtained at weekly intervals occurs in those who spontaneously abort compared with those who do not. The results of this investigation revealed no statistically significant difference in serum CA 125 levels between women who spontaneously aborted and those who successfully completed the first trimester of pregnancy. Even among patients with high levels of CA 125 (>150 U/ml) no statistically significant difference was seen between aborters and controls.

The source of elevated CA 125 levels in maternal serum has been the subject of considerable interest. High concentrations of CA 125 are present in amniotic fluid, but little of the antigen is found in cord blood or fetal urine.^{12,13} Immunohistochemical techniques and assays of decidual homogenates have isolated the antigen to the amnion and decidua.¹⁴⁻¹⁸ It has been hypothesized that an intact epithelial basement membrane within the decidua largely isolates the CA 125 antigen within the amniotic cavity; however, disruption of the membrane may allow the antigen to egress from the amniotic cavity and gain access to the maternal circulation.⁸ Witt et al.¹² studied CA 125 levels in patients with asymptomatic and symptomatic abortion. Although they found a small increase in serum CA 125 levels in patients with vaginal bleeding who ultimately miscarried, lower CA 125 levels were seen in those without bleeding who ultimately had spontaneous abortion. These authors hypothesized that release of the antigen accounted for high levels of CA 125 in the symptomatic group, whereas faulty implantation produced low levels of maternal serum CA 125 in the asymptomatic patients, who eventually aborted.¹²

Although this study did not attempt to follow up patients with threatened abortions separately, no increase in serum CA 125 levels was seen in the week before abortion in patients who aborted. These data suggest that release of the antigen from the decidua is not detected in the maternal circulation in the days before miscarriage.

Check et al.⁹ observed that very high levels of CA 125 appeared to be associated with fetal chromosomal abnormalities. In the current study the patient with the highest serum CA 125 level (1060 U/ml at 7 gestational weeks) occurred in a patient with ovarian hyperstimu-

lation who was delivered of a normal female infant; an amniocentesis performed earlier in the pregnancy revealed a 46,XX karyotype. In addition, Spencer¹⁹ examined maternal serum samples from patients carrying fetuses with trisomy 21 and found that there was no difference in maternal CA 125 levels between women carrying trisomic fetuses and those carrying normal fetuses.

In interpreting the results of this study it should be noted that the patients reported here were all seen in fertility units with a history of infertility or habitual abortion. It is unlikely, but possible, that such a population may differ from a normal, fertile population with respect to CA 125 levels. Consequently, these results should be interpreted with some caution in a more generalized population.

In summary, this prospective study of maternal serum CA 125 levels in early pregnancy indicates that there is no difference in the level of CA 125 between women who spontaneously abort and those who do not abort in the first trimester. Furthermore, this study provides no evidence that very high levels of CA 125 are associated with spontaneous abortion or, in the case of the highest levels, with fetal chromosomal abnormalities. Taken together, these data do not support a role for the measurement of CA 125 levels in early gestation to predict spontaneous abortion.

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