

# Serum CA 125 Levels in Early Pregnancy and Subsequent Spontaneous Abortion

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CA 125 has been found in high concentrations in human amniotic fluid throughout gestation, with significant quantities seen in the decidua and chorion. Because disruption of the epithelial basement membrane of the fetal membrane or the decidua could theoretically lead to a rise in maternal CA 125 levels, this increase may be a predictor of subsequent spontaneous abortion of the fetus. A study was initiated to investigate whether a sudden rise in the serum CA 125 level might predict spontaneous first-trimester abortions. CA 125 levels of 101 pregnant women were evaluated 18–22 days from conception and 6 weeks from conception (a frequent time for spontaneous abortion) to determine whether there is a sudden increase (from baseline or early trimester levels) during the middle or late first trimester immediately before or at the time of abortion. The results indicated that although there was a definite correlation found between elevation of CA 125 and spontaneous abortion, the higher levels occurred early in the first trimester whereas the majority of abortions did not occur until much later, after fetal viability was established. Six of ten women with CA 125 levels of 150 U/mL or greater aborted, compared with four of 92 women with CA 125 levels less than 150 U/mL. One of 11 women pregnant after in vitro fertilization had a CA 125 level above 150 U/mL, and she aborted. (*Obstet Gynecol* 75:742, 1990)

The cancer antigen CA 125, discovered by using monoclonal antibodies raised against cells derived from the ovarian cancer cell line OVLA 433,<sup>1</sup> is present in high concentrations in human amniotic fluid throughout gestation.<sup>2</sup> Extracts of human decidua and chorion have been found to contain significant quantities of CA 125.<sup>3</sup> In contrast, the serum CA 125 level is low in

either maternal or fetal blood, and very little is found in extracts of amnion and trophoblast.<sup>3</sup>

CA 125 has been localized to the apical surfaces of glandular epithelium. It is also found in the secretory products of endometrial glands in proliferative and secretory endometrium as well as in the decidua vera.<sup>3</sup> During the first trimester of pregnancy, the maternal serum levels of CA 125 rise modestly, frequently reaching an average of 85 U/mL,<sup>4</sup> and then drop during the second and third trimesters to the range found in nonpregnant women (20–25 U/mL).<sup>3</sup> Amniotic fluid levels, by contrast, increase during the first two trimesters of pregnancy.<sup>3</sup> Whether the source of CA 125 is fetal membranes or decidua (some recent data suggest the periderm may be the source for early CA 125 elevation),<sup>5</sup> the antigen seems to be distributed preferentially within the amniotic fluid and excluded from the maternal vascular compartment.

In a recent investigation, Quirk et al<sup>3</sup> hypothesized that decidual CA 125 gains access to the maternal compartment via a "tubal reflux," resulting in subsequent absorption via the peritoneal lymphatics. They speculated further that the drop in maternal serum CA 125 may well be related to a functional obstruction of the tubes that occurs as pregnancy advances, with fusion of the decidua capsularis and the decidua parietalis.

Although the CA 125 level in the fluid of benign and malignant serous and mucinous ovarian cysts is high, there is a poor correlation with serum CA 125 levels.<sup>6</sup> One prevailing theory is that the large CA 125 molecules from the cyst fluid gain access to the serum compartment only after the epithelial basement membrane is disrupted.<sup>6</sup>

We conducted a study to investigate the hypothesis that some impending abortions may be associated with disruption of the epithelial basement membrane of either the fetal membrane or the decidua, leading to an increase in maternal serum CA 125. Serum CA 125

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levels 18–22 days from conception, which were assumed would be normal for pregnancy, were compared with levels measured 6 weeks from conception. We wanted to observe these levels during the first trimester to determine whether a sudden rise to abnormally high levels correlated with spontaneous first-trimester abortions. Unfortunately, there were insufficient funds to obtain CA 125 levels weekly, so we arbitrarily chose 6 weeks from conception as a time at which we frequently see abortions in our practice.

### Materials and Methods

One hundred one consecutive pregnant women were evaluated. All presented initially because of infertility; those seeking help for habitual abortion were not included. CA 125 levels were measured 18–22 days from conception and again at 6 weeks from conception. Because a CA 125 level of 65 U/mL is generally considered elevated for nonpregnant women and one of 85 U/mL is average for pregnancy, we considered a level of 150 U/mL or higher (85 + 65) as elevated for pregnancy. Further study included evaluation of serum CA 125 levels in 11 in vitro fertilization (IVF) pregnancies in 11 patients. Our objectives were as follows: 1) to learn more about the origin of the increased early trimester serum CA 125 levels in aborters, and 2) to determine whether the replacement of multiple embryos would increase mean serum CA 125 levels for IVF pregnancies when compared with the CA 125 levels of non-IVF pregnancies.

Chi-square analysis, with Yates correction for discontinuity when appropriate, was used to measure the relationship between levels of CA 125 for aborters compared with non-aborters. Statistical significance was defined as  $P \leq .05$ . The CA 125 assay used was a simultaneous sandwich, solid-phase radioimmunoassay system (Centocor, Inc., Malvern, PA). The assay was performed on an individual basis each time the serum sample was obtained. Inter-assay variation as cited by the manufacturer has been found to be less than 15% coefficient of variation.

### Results

Comparing the CA 125 levels in aborters with those in non-aborters at 18–22 days and 6 weeks from conception gave the following results. Of the 101 consecutive pregnancies, nine women had high CA 125 levels 18–22 days from conception, with five (55.5%) aborting, and 92 women had CA 125 less than 150 U/mL at the same time, with four aborting (4.3%). A statistically significant positive correlation between higher CA 125 levels and spontaneous abortion was indeed found,

but not as expected ( $P < .01$ ). Although the CA 125 elevation occurred during the early first trimester, the majority of abortions (four of five) did not occur until late in the first or early into the second trimester, after fetal viability was established by pelvic sonography.

Evaluation of serum CA 125 levels in the 11 IVF cycles showed that the mean level 15 days post-embryo transfer for ten IVF pregnant women was  $55.2 \pm 35.8$  U/mL (one woman was not included because her level of over 2000 U/mL would skew the mean). The mean CA 125 level of 101 non-IVF pregnancies was  $51.9 \pm 67.3$  U/mL. However, there were no significant differences in the serum CA 125 levels in IVF compared with non-IVF pregnancies, despite the replacement of four embryos in IVF pregnant women with patent tubes.

We believe that the CA 125 level of 2180 U/mL in the 11th IVF patient is the highest ever recorded in a pregnant patient. This level was measured 15 days after the transfer of four embryos. Fetal viability was confirmed at 5 weeks from transfer and, at that time, the serum CA 125 level measured 275 U/mL. However, repeat sonography at 7 weeks from transfer no longer demonstrated fetal viability. The sac measured  $21 \times 12 \times 15$  mm, consistent with 6.6 weeks, and the crown-rump length was 12 mm, consistent with 7.2 weeks from transfer. The serum CA 125 level had dropped to 61 U/mL when fetal death was diagnosed, and eventually decreased to 12 U/mL 2 weeks after evacuation. Chromosomal analysis of the fetal products revealed 45,X, consistent with Turner syndrome. In all abortion cases, CA 125 returned to levels less than 35 U/mL within 1 month of the abortion.

Only one of the ten IVF pregnant patients aborted when the CA 125 level was below 150 U/mL. Among patients with a level in excess of 150 U/mL, there was only one abortion and again, this occurred after the demonstration of fetal viability. Considering the IVF and non-IVF patients as one group, six of ten women who had levels of 150 U/mL or higher aborted. Five of six women aborted despite demonstrating fetal viability when CA 125 was increased, whereas only five of 112 aborted when the CA 125 was less than 150 U/mL, even though none of these demonstrated fetal viability.

### Discussion

We have previously demonstrated that once fetal viability is established, only 3.7% of pregnant women abort by 20 weeks.<sup>7</sup> Whenever we were able to perform chromosomal studies of aborted fetuses, we found a high percentage of chromosomal abnormalities.

Considering the long delay in fetal death from the

first high CA 125 level measured and that the patient with an extremely high CA 125 level (over 2000 U/mL) did have a karyotype associated with fetal anomalies leads us to speculate that anomalies may in some way stimulate an early rise in CA 125. That the CA 125 levels returned to normal after spontaneous abortion eliminated the possibility that some other condition caused the marked increase. Although elevated CA 125 levels have been found previously in patients suffering from ovarian hyperstimulation syndrome,<sup>8</sup> there were no patients with this syndrome in our study. Further evidence against the possibility that high CA 125 levels merely reflect an increase in follicles and possible embryos was the demonstration of similar mean CA 125 levels in patients conceiving after IVF with the replacement of four embryos.

If further studies confirm these preliminary findings, perhaps a CA 125 serum test should be obtained along with the initial  $\beta$ -hCG level and, if it is over 150 U/mL, chorionic villus sampling or amniocentesis might be recommended. Furthermore, even if fetal viability has been established at 7-8 weeks' gestation, high CA 125 levels should prompt a repeat fetal ultrasound during the first trimester. Because by 6 weeks from conception the CA 125 levels in aborters could not be distinguished easily from those of non-aborters, we do not believe that taking measurements this late is of any value. Thus, from a practical standpoint, because most obstetric patients present much later than 18-22 days from conception, the potential usefulness of screening for chromosomal abnormalities might be restricted predominantly to infertility patients, for whom pregnancy tests are done early. However, if a definite predictive value of chromosomal defects could be confirmed, obstetricians could promulgate information about the importance of obtaining earlier CA 125 levels, and this may influence some women to be

evaluated much earlier for pregnancy than they would have been otherwise.

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