Value of serum CA-125 concentrations as predictors of pregnancy in assisted reproduction cycles

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The means by which endometrial receptivity influences conception rates in assisted reproductive technology (ART) is poorly understood. As the glycoprotein CA-125 is a product of human endometrium and is measurable in the peripheral circulation, it was investigated whether it might serve as an indicator of endometrial receptivity and predictor of pregnancy. In this prospective study, serum CA-125 concentrations of 75 ART cycles were measured 1 day before and on the day of human chorionic gonadotrophin (HCG) administration, and on the day of oocyte retrieval. These women did not have endometriosis and were induced by long-protocol gonadotrophin-releasing hormone analogue. Pregnancy was achieved in 35 (46.7%) cycles, but not in 40 cycles (53.3%). Serum CA-125 concentrations 1 day before and on the day of HCG administration and on the day of oocyte retrieval were significantly higher in cycles with pregnancy than in those without pregnancy ($P < 0.05$). It was noted that CA-125 concentrations on the day of oocyte retrieval were the best predictors of pregnancy, with concentrations $>10$ IU/ml having an accuracy of 86.6% for pregnancy. In conclusion, in intracytoplasmic sperm injection cycles, women with high serum CA-125 concentrations ($>10$ IU/ml) on the day of oocyte retrieval had very high pregnancy rates.

Key words: assisted reproduction treatments/CA-125/endometrium/pregnancy/receptivity

Introduction

In the clinical practice of human IVF, the majority of pregnancy failures occur after embryo transfer. Although the majority of patients undergoing IVF have oocyte retrieval, and an acceptable fertilization and cleavage rates of embryos, only a small proportion of the transferred embryos actually implant and result in viable pregnancies.

There are probably two factors that have a major effect on the decrease in implantation rates of human embryos: chromosomally or morphologically abnormal embryos; and/or non-receptive endometrium (Paulson et al., 1990; Munné et al., 1995). Thus, a marker that could predict uterine receptivity would be very useful in deciding whether to proceed with embryo transfer or to culture the embryos and then to cryopreserve and transfer them in a later cycle.

Endometrial thickness (Gonen et al., 1989), pre-embryo secretions (Daya et al., 1986) and the identification of uterine secretory proteins (Beier-Hellwing et al., 1989) have been evaluated as indicators of uterine receptivity. It has also been shown (Ilesanmi et al., 1993) that endometrial progesterone receptors and one of the integrin cell adhesion molecules might be indicators of the receptive state.

Although CA-125 is a well-established ovarian tumour marker, this glycoprotein is also produced by the endometrium of naturally ovulating women, and is measurable in the peripheral circulation (Brumsted et al., 1990; Abaé et al., 1992; Zeimet et al., 1993). Therefore, CA-125 can be regarded as an indicator of endometrial receptivity and a predictor of pregnancy.

This prospective study was carried out to investigate the relationship between serum CA-125 concentrations before embryo transfer and the clinical outcome of that assisted reproductive treatment (ART) cycle.

Materials and methods

In this prospective study, data were collected from women who attended the ART programme at the Family Planning and Infertility Research and Treatment Center, Ege University, Izmir, Turkey, during the period between March and September 1998.

Only women undergoing intracytoplasmic sperm injection (ICSI) cycles who were confirmed laparoscopically to have no endometriotic implants, induced by long-protocol gonadotrophin-releasing hormone (GnRH) analogue and FSH + human menopausal gonadotrophin (HMG) combinations, and had embryo transfer were included in the study.

Pituitary desensitization was started in the early follicular phase (second day of the menstrual cycle) with daily administration of triptorelin (Decapeptyl®; Ferring, Kiel, Germany). Triptorelin 0.5 mg/day s.c. was given for 7 days, followed by 0.1 mg/day s.c. for another 7 days. Down-regulation was maintained by using only GnRH analogue for 14 days. If the serum oestradiol concentrations were $<70$ pg/ml and transvaginal ultrasonography revealed no ovarian cyst...
ACS:180 OV assay for CA-125 is a two-side sandwich immunoassay were signi-

The characteristic of the study populations are compared between the two groups in Table I. Peak serum oestradiol concentrations (pg/ml) and the number of transferred embryos were significantly higher in cycles with pregnancy compared with cycles with no pregnancy (respectively 2022 ± 114.84 versus 1483.17 ± 129.9 pg/ml and 4.66 ± 0.3 versus 3 ± 0.3 embryos; t-test, P < 0.05), whereas the other parameters did not show any significant difference between groups (Table II).

CA-125 concentrations from sera on the day before and on the day of HCG administration, and on the day of oocyte retrieval, for measurement of serum CA-125 concentrations. The blood samples were centrifuged (2000 g for 20 min) and stored at −20°C (<5 days). Serum CA-125 and oestradiol were determined by using an automated chemiluminescence system (Chiron Diagnostics ACS:180, Fernwald, Germany; range for CA-125 and oestradiol 1.7–1000 IU/ml and 10–3000 pg/ml respectively). The Chiron Diagnostics ACS:180 OV assay for CA-125 is a two-side sandwich immunoassay with directchemiluminometric technology, which uses two purified monoclonal mouse antibodies specific for CA-125. The intra-assay and inter-assay coefficients of variation (CV) for CA-125 were 4.9 and 5.8%, and for oestradiol were 6 and 12% respectively. The mean recovery was 99.5%. This is a second-generation assay for CA-125 utilizing both the OC125 and M11 epitopes, and yielding an improved assay range (Kenemans et al., 1993, 1995; Bonfret et al., 1994).
CA-125 to predict pregnancy in assisted reproduction

Table II. Laboratory characteristics of the pregnant and non-pregnant groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-pregnant</th>
<th>Pregnant</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of oocytes retrieved&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.58 ± 1.02</td>
<td>9.54 ± 0.92</td>
<td>NS</td>
</tr>
<tr>
<td>No. of mature oocytes&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.98 ± 0.58</td>
<td>6.43 ± 0.54</td>
<td>NS</td>
</tr>
<tr>
<td>Grade I embryo rates (%)</td>
<td>47.5</td>
<td>54.3</td>
<td>NS</td>
</tr>
<tr>
<td>No. of embryos transferred&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.0 ± 0.3</td>
<td>4.66 ± 0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak oestradiol conc. (pg/ml)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1483.17 ± 129.9</td>
<td>2002.3 ± 114.8</td>
<td>0.004</td>
</tr>
<tr>
<td>Endometrial thickness (mm)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12.6 ± 0.38</td>
<td>13.45 ± 0.42</td>
<td>NS</td>
</tr>
</tbody>
</table>

<sup>a</sup>Values are mean ± SEM.
<sup>b</sup>Conversion factor to SI unit, 3.67.
NS = not significant (t-test and χ² test; P > 0.05).

significantly higher in the pregnant versus the non-pregnant group (t-test, P < 0.05) (Table III). While a positive correlation was found between serum CA-125 concentrations and the number of embryos transferred (r = 0.23, P = 0.04), there was no correlation between CA-125 concentrations and peak oestradiol concentrations (r = 0.1, P = not significant (NS)), the number of oocytes retrieved (r = 0.007, P = NS), embryo quality (r = –0.1, P = NS) or endometrial thickness (r = 0.05, P = NS).

A mathematical model was formed by using logistic regression analysis and forward selection method to determine the best sampling day and the CA-125 concentrations that best discriminated cycles which resulted in no pregnancy from those that resulted in pregnancy. In this model, the day of oocyte retrieval was found as the best sampling day, and CA-125 concentrations >10 IU/ml as the best cut-off value predictive of pregnancy. A comparison of the predictive variables for the three sampling dates is shown in Table IV. Serum CA-125 concentrations on the day before and on the day of HCG administration were less highly predictive for pregnancy than on the day of oocyte retrieval. Only one cycle (3.7%) with a CA-125 concentration >10 IU/ml on the day of oocyte retrieval did not result in pregnancy.

All of the cycles resulting in pregnancy had CA-125 concentrations ≥15 IU/ml, while there were no pregnancies for CA-125 concentrations ≤5 IU/ml on all of the three sampling days. The positive predictive values for serum CA-125 concentrations grouped as ≤5, 6–10 and >10 IU/ml for the three sampling days are presented in Table V.

Discussion

Synthesis of CA-125 is not restricted to malignant transformation; rather it is also expressed in benign ovarian tumours (Kabawat et al., 1983; Barbieri et al., 1986) and in normal tissues such as the endocervix, endometrium and Fallopian tube, and in mesothelial cells lining the adult pleura, pericardium and peritoneum (Kabawat et al., 1984; Zeimet et al., 1993, 1998). The highest concentrations of CA-125 were measured in uterine and cervical fluids of healthy women (Crombach et al., 1989; Martinez et al., 1994). The origin of cyclic changes in CA-125 serum concentrations in healthy women remains to be clarified. The CA-125 amounts responsible for cyclic changes in serum concentrations in normally menstruating women seem to be a product of normal endometrium (Zeimet et al., 1993). It was indicated (Zeimet et al., 1993) that steroid hormones or possibly paracrine factors in the normal endometrium are involved in the regulation of CA-125 synthesis and release. These authors also found that CA-125 tissue content decreases with increasing oestradiol concentrations during the proliferative phase to lowest concentrations at the time of high progesterone activity (early secretory phase), and showed that CA-125 expression is differently regulated in the basalis and functionalis layers of the endometrium.

In another report (Gurgan et al., 1993), it was suggested that the ovaries were the main source of CA-125 production, although the study group consisted of only five patients who were not infertile and did not receive ovulation induction. Nonetheless, these data do not exclude the idea of the ovaries being a major source or a major component of CA-125 production. On the contrary, it was suggested (Weintraub et al., 1990) that the main source of CA-125 is the endometrium, while others (Ozaksit et al., 1993) reported that there was a correlation between the high concentrations of oestradiol, endometrial thickness and CA-125 concentrations during midcycle and mid-luteal phase in patients with ovarian hyperstimulation syndrome.

It was also reported (Mordel et al., 1992) that CA-125 existed in significant amounts in the follicular fluid of periovulatory follicles of IVF and embryo transfer patients, but that there was no correlation between CA-125 concentrations and follicular fluid oestradiol, progesterone, testosterone, oocyte fertilization, embryo quality or pregnancy rates. It was stated that a possible ovarian tissue–blood barrier might preclude the passage of CA-125 from the follicular fluid to the serum (Fleuren et al., 1987); hence the measured serum CA-125 concentrations may not reflect the true follicular fluid CA-125 synthesis.

On the other hand, it was demonstrated (Lanzone et al., 1990) that serum CA-125 concentrations remained stable at all phases of the natural or stimulated cycles, and did not reflect the effect on pregnancy outcome. Others (Zweers et al., 1990) observed a significant high concentration of serum CA-125 only in the luteal phase of women after ovarian stimulation for IVF only.

On the basis of these studies it was concluded that serum CA-125 concentrations might originate at least partly from the endometrium. Therefore, an investigation was performed to determine whether such concentrations could reflect endometrial receptivity and thus be predictive of pregnancy before embryo transfer in ART cycles. Only GnRH analogue downregulated cycles were examined in order to avoid the increase in CA-125 during menses. Because women with endometriosis have elevated CA-125 concentrations (Pittaway and Fayez, 1986), the women without endometriosis were examined. Also, the cycles were examined before the ovarian trauma and intrauterine spillage of follicular fluid during and after oocyte retrieval.

In this study, it was found that in GnRH analogue down-
the peak oestradiol concentrations were found to be significantly higher in the pregnant group. This finding suggests that serum CA-125 concentration predicts pregnancy independent of the peak serum oestriadiol concentration. However, these varying results may also be due to the small sample number and different laboratory analytical systems that are used to measure different epitopes.

Although increased pre-retrieval endometrial thickness has been found to be associated with higher pregnancy rates (Gonen et al., 1989; Bersinger et al., 1998), the current study confirmed the previously published finding (Oliveira et al., 1997) that endometrial thickness did not show any significant difference between pregnant and non-pregnant groups. Provided that it exceeds 7 mm, endometrial thickness is not a prognostic parameter in IVF (Oliveira et al., 1997). Others (Yuval et al., 1999) also reported that there was no correlation between endometrial thickness and IVF success rates.

Recently, some authors have evaluated serum CA-125 concentrations as predictors of pregnancy before embryo transfer in IVF-embryo transfer cycles. One group (Miller et al., 1996) examined 56 down-regulated cycles (25 pregnant, 31 non-pregnant), and found that higher serum CA-125 concentrations in the luteal phase on the day before and the day of embryo retrieval showed any prognostic significance. As such, CA-125 concentrations >10 IU/ml on the day of HCG administration were the best predictors of pregnancy.

It was also reported that serum CA-125 concentrations on the day of oocyte retrieval were significantly higher in cycles with pregnancy, whereas there was no significant change in follicular fluid CA-125 concentration (Chryssikopoulos et al., 1996).

In contrast, others (Brandenberger et al., 1998) suggested that neither the serum CA-125 concentrations nor their increase on the day of HCG until the day of embryo transfer showed any prognostic significance to the outcome of IVF-embryo transfer. Another recent report (Noci et al., 1999) revealed that CA-125 concentrations on oocyte retrieval day were lower in pregnancy cycles. The current results are in parallel with those of two groups (Chryssikopoulos et al., 1996; Miller et al., 1996), but at variance with the results of other groups (Brandenberger et al., 1998; Noci et al., 1999). In all these studies, the study groups consisted of different infertility aetiologies such as male factor, tubal

### Table III. Comparison of serum CA-125 concentrations (IU/ml) of the three sampling days between the pregnant and non-pregnant groups

<table>
<thead>
<tr>
<th>Sample timing</th>
<th>Non-pregnant</th>
<th>Pregnant</th>
<th>( P^b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day before HCG</td>
<td>6.04 ± 0.38 (0.74 ± 0.03)</td>
<td>14.14 ± 1.81 (1.06 ± 0.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>administration(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day of HCG</td>
<td>5.92 ± 0.36 (0.74 ± 0.03)</td>
<td>14.26 ± 1.63 (1.08 ± 0.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>administration(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day of oocyte retrieval</td>
<td>5.90 ± 0.39 (0.73 ± 0.03)</td>
<td>15.94 ± 1.59 (1.15 ± 0.03)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\(^a\)Values are mean ± SEM.
\(^b\)t test.

### Table IV. Comparison of predictive variable for pregnancy among the three sampling days

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sampling day (CA-125 concentration &gt;10 IU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day before HCG administration</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>57.1</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>95</td>
</tr>
<tr>
<td>Positive predictive value (%)</td>
<td>90</td>
</tr>
<tr>
<td>Negative predictive value (%)</td>
<td>71.7</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>77.3</td>
</tr>
</tbody>
</table>

HCG = human chorionic gonadotrophin.

### Table V. Positive predictive values for pregnancy on the three sampling days according to the different CA-125 concentrations

<table>
<thead>
<tr>
<th>Sample timing</th>
<th>CA-125 concentration (IU/ml)</th>
<th>( \leq 5 )</th>
<th>6–10</th>
<th>&gt;10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day before HCG</td>
<td>15.8</td>
<td>35.3</td>
<td>90.9</td>
<td></td>
</tr>
<tr>
<td>administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day of HCG administration</td>
<td>6.3</td>
<td>33.3</td>
<td>95.7</td>
<td></td>
</tr>
<tr>
<td>Day of oocyte retrieval</td>
<td>0</td>
<td>25.7</td>
<td>96.3</td>
<td></td>
</tr>
</tbody>
</table>

HCG = human chorionic gonadotrophin.
factor, endometrial factor and endometriosis. In the current study, the group mainly consisted of andrological factor, and this may have influenced the different results. In contrast to an earlier study (Noci et al., 1999), the present investigation was designed prospectively, and only ICSI cycles in which the endometria were more likely to be normal were evaluated. The ovulation-inducing drugs used were also different in all of these studies, and this might affect the different outcomes. Another parameter (referred to earlier) was the different laboratory methods used to measure different epitopes. The second-generation assay used in the current study detected CA-125 via antibodies directed to the OC125 and M11 epitopes, and this resulted in an improved assay range (Kenemans et al., 1993, 1995; Bonfrer et al., 1994). The results (Noci et al., 1999) that were contradictory to those of the current study were obtained using a different second-generation assay for CA-125 detection. In addition, the abortion rates should be compared in these different studies, as this might clarify some of the different results obtained. In the current study it was observed that, of 35 pregnancies, 10 failed to continue—an effect which may also reflect the higher CA-125 concentrations.

Consequently, it could be said that endometrial receptivity is an important factor in IVF pregnancy success, and may be the origin of the changes in serum CA-125 that occur mostly from the endometrium. An earlier study (Bersinger et al., 1993) investigating the considerable contribution of the endometrium to serum CA-125 concentrations supports this hypothesis. Accordingly, the serum CA-125 concentrations reflect a favourable endometrium. The ability to predict the chances of pregnancy before embryo transfer might assist clinicians in deciding whether embryos have a greater chance of implantation if they are transferred in a subsequent cycle.

Whatever the source or the role of CA-125 is, a high predictive value of serum CA-125 with concentrations >10 IU/ml on the day of oocyte retrieval for pregnancy was observed in the current study. As yet, the ratio of the contribution of different sources to the CA-125 that is measured in the peripheral circulation cannot be determined. However, when this becomes possible, prospective studies should be able to explain whether CA-125 that originates from the ovaries or endometrium (or both) is predictive of successful outcome in ICSI cycles.

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References


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