Tumour marker – HE4 and CA125 in ovarian cancer detection

The ideal tumour marker for epithelial ovarian cancer screening in the asymptomatic female population has not yet been realised, but the identification and use of HE4 in combination with CA125 has improved the accuracy of tests for diagnosis and management of women with an ovarian/adnexal mass. Screening women with a strong family history of ovarian malignancy will be an extension of this new combination.

Ovarian cancer is the fourth most common cause of cancer-related deaths in women worldwide. The symptoms relate to the mass effects on the ovary and surrounding tissues, but otherwise are often vague and non-specific. Perhaps as many as 10% of women in Australia, at some time in their life will undergo investigation for an ovarian or adnexal mass. Of the masses that are examined histologically, 10–20% will be found to harbour an ovarian cancer. More than half of all primary ovarian cancers will be serous epithelial carcinomas. The other, less frequent, types of primary ovarian malignancies include mucinous type ovarian carcinoma, germ cell carcinoma and granulosa cell tumour. These can be managed with other tumour markers (e.g. CEA, CA72-4; hCG; inhibin B and Anti-Mullerian Hormone). Metastatic malignancy to the ovary is not uncommon and should be suspected with bilateral ovarian masses.

HE4, Human Epididymis 4 protein, was first identified in males in the distal epithelium of the epididymis. It functions as a protease inhibitor essential for sperm maturation. It has since been found in other healthy epithelial tissues such as the respiratory tract and female reproductive organs, including the ovaries and uterus, where its function is not fully elucidated. It is normally secreted only in very low concentrations by healthy ovaries.

HE4 is found in high levels in the serum of women with serous epithelial ovarian cancer. Serum levels are less affected by menstruation, ovulation and other benign ovarian conditions (e.g. endometriosis) compared with CA125. In pre-menopausal women, HE4 is the more sensitive and specific marker of ovarian malignancy, including early stage ovarian cancer. In post-menopausal women, the very non-specificity of CA125 can be helpful in determining whether an ovarian mass is malignant or not, as the incidence of secondary malignancy to the ovary in this group of women is more common, and the occurrence of minor rises due to benign ovarian conditions is less likely. CA125 however, can be quite elevated in conditions such as pulmonary embolus; cirrhosis; peritoneal dialysis; and pleural, pericardial and peritoneal effusions.

In a study evaluating multiple biomarkers for ovarian cancer, the combination of CA125 and HE4 was superior compared with any other marker alone or 2 markers in combination (Moore 2008).

<table>
<thead>
<tr>
<th>Estimates of Sensitivity</th>
<th>Benign vs Ovarian Cancer: Sensitivity at 90% Specificity</th>
<th>95% Specificity</th>
<th>98% Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA125</td>
<td>61.2%</td>
<td>43.3%</td>
<td>23.9%</td>
</tr>
<tr>
<td>HE4</td>
<td>77.8%</td>
<td>72.9%</td>
<td>64.2%</td>
</tr>
<tr>
<td>CA125 + HE4</td>
<td>80.7%</td>
<td>76.4%</td>
<td>71.6%</td>
</tr>
<tr>
<td>CA125 + HE4 + SMRP*</td>
<td>80.6%</td>
<td>74.7%</td>
<td>71.7%</td>
</tr>
<tr>
<td>CA125 + HE4 + CA72-4</td>
<td>82.1%</td>
<td>78.8%</td>
<td>71.5%</td>
</tr>
</tbody>
</table>

*soluble mesothelin-related peptides
The Risk of Ovarian Malignancy Algorithm (ROMA) is a calculation combining the results of the CA125 and the HE4; the algorithm classifies women as being at low or high risk for malignant disease. This risk is given as an adjunct to the two test results for CA125 and HE4. ROMA calculates the risk of finding ovarian cancer during surgery.

Another use of HE4 is as a tumour marker for endometrial carcinoma, however, with less efficiency than that currently demonstrated for ovarian cancer.

**Reference range:**
- HE4 <70 p
- CA125 <35 IU/L
- ROMA
  - <7.4% Pre-menopausal patients
  - <25.3% Post-menopausal patients

**What to order:**
- HE4 and CA125 or ROMA (preferred)

**Sample:**
- Serum

**Method:**
- HE4 & CA125 immunoassays
  - (Abbott Architect)

**Timing:**
- Days 7-10 of menstrual cycle

**Cost:**
- $46 (no rebate for HE4)

**Reference**