

## **CA125 (serum)**

### **1 Name and description of analyte**

- 1.1 Name of analyte  
Cancer Antigen 125 (CA125)
- 1.2 Alternative names  
Mucin-16
- 1.3 NLMC code  
To follow
- 1.4 Description of analyte  
CA125 is an antigenic determinant on a high molecular weight mucin-like glycoprotein. It is recognised by the monoclonal antibody OC125, which was raised using an ovarian cancer cell line as an immunogen. CA125 is expressed by epithelial ovarian tumours and various other pathological and normal tissues of Müllerian duct origin.
- 1.5 Function of analyte  
The physiological function of CA125 is unknown but some sources suggest that it may provide a lubricating barrier against particles and infectious agents at mucosal surfaces.

### **2 Sample requirements and precautions**

- 2.1 Medium in which measured  
CA125 is measured in serum.
- 2.2 Precautions re sampling, handling etc.  
General precautions only.

### **3 Summary of clinical applications and limitations of measurements**

- 3.1 Uses  
CA125 is the most widely used tumour marker for epithelial ovarian cancer.
  - 1. It is used in the differential diagnosis of ovarian cysts and pelvic masses in postmenopausal women. CA125 should be used in conjunction with transvaginal ultrasound scans (TVUS) for the calculation of the Risk of Malignancy Index (RMI)
  - 2. It is measured in patients with ovarian cancer to assess response to chemotherapy and to detect tumour recurrence.
  - 3. Since the NICE guidelines for the early recognition of ovarian cancer were published in April 2011 (see 9.2), it is now recommended that individuals who present in primary care with symptoms suggestive of ovarian cancer have a CA125 measurement, to determine the need for further investigations including pelvic and abdominal ultrasound scans.
  - 4. It is used to screen women with a family history of hereditary forms of ovarian cancer.

### 3.2 Limitations

At present, the value of screening asymptomatic post-menopausal women for ovarian cancer by measuring CA125 remains uncertain and is not recommended. Results from the current prospective UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) are not expected until 2014. The Prostate, Lung, Colorectal and Ovarian (PLCO) randomised controlled trial in the United States found no decrease in mortality rates as a result of screening with CA125.

## 4 Analytical considerations

### 4.1 Analytical methods

CA125 is measured by immunoassay.

### 4.2 Reference method

None reported.

### 4.3 Reference materials.

An international reference preparation is not currently available.

### 4.4 Interfering substances

As with all immunometric assays, there is a potential for interference by *in vivo* heterophilic antibodies. Results must always be considered in relation to the clinical situation and to previous assay results, if available. The latter is particularly important when serial results are being used for monitoring the response to treatment.

### 4.5 Sources of error

At very high concentrations, there is a risk of generating falsely low values as a result of the high dose hook effect.

## 5 Reference intervals and variance

5.1.1 Reference interval (adults): the upper reference limit is 35 IU/mL but may be higher in pre-menopausal women.

5.1.2 Reference intervals (others): not applicable.

### 5.1.3 Extent of variation

5.1.3.1 Interindividual CV: this is not a useful concept with tumour markers.

5.1.3.2 Intraindividual CV: 29%

5.1.3.3 CV of method: 4% (using QC data. Analysed on Siemens Advia Centaur, 2<sup>nd</sup> generation two-site sandwich immunoassay).

5.1.3.4 Critical difference= 48.7%

### 5.1.4 Sources of variation

Serum [CA125] decreases with aging and after the menopause. [CA125] has been shown to vary 20-50% between different ethnic groups in post-menopausal women, with concentrations being lower in African-American women than in white women. Menstrual cycle variations also occur and [CA125] is raised in pregnancy.

## 6 Clinical uses of measurement and interpretation of results

### 6.1 Uses and interpretation

1. Differential diagnosis of pelvic masses and adnexal cysts

Measurement of CA125 is recommended as an adjunct in distinguishing benign from malignant suspicious pelvic masses, particularly in postmenopausal women. [CA125] is used in conjunction with TVUS to calculate the risk of malignancy index (RMI). [CA125] is multiplied with the ultrasound score (U) and menopausal status (M) to calculate the Risk of Malignancy Index (RMI) score:

$$\text{RMI} = U \times M \times \text{CA125}$$

The RMI forms the basis of patient pathway guidelines for the management of pelvic masses and adnexal cysts.

## 2. Monitoring response to treatment and tumour recurrence.

A persistently increasing CA125 value may be associated with progressive malignant disease, poor therapeutic response or relapse, whereas a declining CA125 value indicates a favourable prognosis and good therapeutic response. The half-life of CA125 is 5-10 days.

## 3. Patients presenting to GPs with symptoms suggestive of ovarian malignancy

Since the publication of NICE guidelines CG122 in April 2011 it is now recommended that CA125 should be measured in women who present to primary care with persistent symptoms (particularly occurring >12 times per month) that are consistent with ovarian cancer. These include abdominal distension, early satiety, loss of appetite, pelvic or abdominal pain and increased urinary urgency and/or frequency. If the serum CA125 is  $\geq 35$  IU/mL, an ultrasound scan of the abdomen and pelvis should be performed with calculation of RMI as above.

## 4. Screening

CA125 is recommended, together with TVUS, for early detection of ovarian cancer in women with hereditary ovarian cancer syndromes, in whom early intervention may be beneficial.

## 6.2. Confounding factors

1. Serum [CA125] is elevated in only 50% of patients in the early stages of ovarian cancer, when treatment is most effective.
2. Specificity is poor: serum [CA125] is raised in a number of other benign and malignant conditions (see 7.1.1)
3. Pre-menopausal women are more likely to have falsely elevated [CA125] levels than post-menopausal women due to either menstruation or pregnancy.

## 7. Causes of abnormal results

### 7.1 High values

#### 7.1.1 Causes

- Gynaecological malignancy
  - epithelial ovarian carcinoma
  - adenocarcinoma of the endometrium
  - carcinoma of the fallopian tube
  - uterus (uncommonly).
- Other malignancies
  - Colon, rectum
  - liver
  - lung
- Non-malignant conditions, e.g.
  - pregnancy

- menstruation
- ascites
- peritoneal or pleural inflammation
- benign ovarian cysts
- endometriosis
- uterine fibromyomata (fibroids)
- pelvic inflammatory disease
- cirrhosis.

During menstruation [CA125] can increase 2–3 fold; it can increase to  $\geq 1000$  IU/mL in patients with ascites.

#### 7.2.2 Investigation

CA125 should only be measured when there is a clinical suspicion of ovarian cancer or a patient is at high risk of ovarian cancer. Further investigations will depend on the clinical context but may need to include exclusion of non-malignant conditions as well as investigations directed towards diagnosing ovarian cancer (particularly ultrasound).

### 7.2 Low values

#### 7.2.1 Causes

CA125 should be undetectable or present in only very low concentrations in healthy individuals; the concept of a low value is not applicable.

#### 7.2.2 Investigation

Not applicable.

### 7.3 Notes

None

## 8. Performance

- 8.1 Medeiros *et al* (2009) (see 9.1) conducted a systematic review and meta-analysis of CA125 measurement for the discrimination of malignant/borderline malignant tumours from benign tumours in women with clinically suspected adnexal masses. Using a threshold [CA125] of 35 U/mL to signify malignancy, the sensitivity and specificity of CA125 was estimated as 80% (95% CI 76-82%) and 75% (95% CI 73-77%), respectively. Similarly, in their systematic review of 46 studies, Myers *et al* (2006) (see 9.1) estimated the sensitivity and specificity of CA125 as 78% (95% CI 75-81%) and 78% (95% CI 71-82%), respectively.

## 9. Systematic reviews and guidelines

### 9.1 Systematic reviews

1. Medeiros LR, Rosa DD, da Rosa MI, Bozzetti MC. Accuracy of CA125 in the diagnosis of ovarian tumours: a quantitative systematic review. *Europ J Obstets Gynecol Reprod Biol* 2009;142:99-105.

*A quantitative systematic review to estimate the accuracy of CA125 assay in the diagnosis of ovarian tumors. A total of 17 studies were included that evaluated CA125 levels for the diagnosis of ovarian tumors and compared them with paraffin-embedded sections as the diagnostic standard.*

2. Myers ER, Bastian LA, Havrilesky LJ *et al*. Management of adnexal mass. *Evid Rep Technol Assess* 2006;130:1-145.

*This systematic review evaluated the major diagnostic strategies for distinguishing benign from malignant adnexal masses. These included*

*bimanual pelvic examination, ultrasound (morphology and Doppler velocimetry), MRI, CT, FDG-PET, CA125, and scoring systems that incorporated multiple clinical, laboratory, and radiologic findings. Meta-analysis using a random-effects model was used to estimate pooled sensitivity and specificity for discriminating benign from malignant masses.*

## 9.2 Guidelines

1. NICE guideline 122: The recognition and initial management of ovarian cancer, 2011. See: <http://guidance.nice.org.uk/CG/122> (last accessed 15.3.12).
2. Sturgeon CM, Duffy MJ, Stenman UH, *et al.* National Academy of Clinical Biochemistry laboratory medicine practice guidelines for use of tumor markers in testicular, prostate, colorectal, breast, and ovarian cancers. *Clin Chem* 2008;12:11-79.

## 9.3 Recommendations

The National Academy of Clinical Biochemistry (NACB) guidelines (See 9.2) recommend that if CA125 is used in monitoring treatment, the first sample should be taken within 2 weeks prior to treatment with subsequent samples at 2–4 weeks during treatment and at intervals of 2–3 weeks during follow-up. The same assay method should be used throughout and patients with anti-CA125 antibodies cannot be evaluated.

## 10 Links

### 10.1 Related analytes

None

- 10.2 Related tests Human epididymis protein (HE4) is another marker of epithelial ovarian cancer and can be used in a predictive model called the Risk of Ovarian Malignancy Algorithm (ROMA) to estimate the risk of epithelial ovarian cancer in women presenting with a pelvic mass. Some studies suggest it has a superior diagnostic performance to CA125 but neither HE4 nor the ROMA model has yet been evaluated in a primary care setting and neither were considered by the NICE guideline development group.

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