

Screening in Ovarian Neoplasm

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Ovarian neoplasm is extremely aggressive and has a high mortality rate among affected women; therefore, the crucial role of screening tests is easy to understand. Prevention and early diagnosis should be essential priorities in the management of this malignancy. Since a complete and correct clinical examination can select the cases that require specialized investigations, we can consider it a first screening test.

Keywords: ovarian neoplasm, the role of screening; prevention and early diagnosis, screening test

Detection of BRCA mutations and genetic testing

Although BRCA 1 and 2 gene mutations have been frequently associated with breast and ovarian neoplasm, cases have been reported in association with tubular, primary peritoneal, colonic and prostate neoplasms.

Screening of ovarian neoplasm by BRCA testing starts with the initial address to the genetics department and the primary screening of the woman with ovarian neoplasm within a family, possibly following the testing of female first-degree relatives, according to the recommendation of ESMO (European Society of Medical Oncology) in the case of the presence of BRAC1 and / or mutations 2. Women who have no family history of ovarian / breast cancer are not directed to perform BRCA testing or genetic counseling [1].

BRCA gene mutations are transmitted autosomal dominant and have a high penetration capacity. What is characteristic of the ovarian neoplasm associated with the presence of BRCA mutation are the following aspects: early onset of the disease, aggressive evolution and aggressive histo-pathological forms [2].

15% of women with epithelial ovarian cancer have inherited BRCA gene mutations. Knowing the status of BRCA (BRCA-ness) is extremely important for the patient with ovarian neoplasm, because in the situation of her presence, she will have PARP and ADP-ribose polymerase inhibitors available as a therapeutic line. Knowing the BRCA-ness status is also extremely important for first-degree relatives, because in the case of proving the carrier state, it will be able to consider, at one point, the surgery to reduce the risk of developing an ovarian neoplasm [3].

Not long ago, it was found that the use of poly ADP-ribose polymerase inhibitors in the treatment of ovarian neoplasm associated with BRCA gene mutations (which represents 15% of the total *high grade ovarian carcinoma*) has beneficial indications for sporadic familial disease [4].

Risk reduction surgery usually involves bilateral anexectomy, but given the fact that these patients are often young, inducing early menopause is an important problem. Currently, there are ongoing studies that attempt to demonstrate the decrease in risk but especially the decrease of anxiety in patients with BRCA mutations only through bilateral salpingectomy [5].

Dosage of tumor markers:

-CA 125

It represents a repetitive epitope protein of MUC-16 with a role in supporting neoplastic cell proliferation and inhibiting the antitumor immune response.

It is the most widely used tumor marker in the screening of ovarian neoplasm.

90% of patients with advanced ovarian neoplasm have elevated concentrations because this marker is released by tumor cells from serum-modified ovarian epithelium through stimulation by alpha TNF and gamma IFN [6].

Because CA 125 can also be secreted by unmodified malignant cells, it may also have increased concentrations in benign pathologies, eg, uterine fibroids, functional or endometriotic ovarian cysts, inflammatory pelvic diseases. Therefore, it cannot be used singly in the screening of ovarian neoplasm. As a reference value, the upper limit of normal is 35 U / mL [7].

Thus, the paraclinical combination between imaging and CA125 dosing is much more useful than single dosing of tumor markers, especially in advanced stages of the disease. For stages I and II of the disease it seems that the imaging investigations were superior to the CA125 dosage for raising the suspicion of malignancy [8].

As it has been shown statistically that ovarian neoplasm has an important recurrence rate (with localization, especially locoregional, intraperitoneal), the CA 125 marker accompanied by imaging investigations (especially PET-CT) is used in the post-operative follow-up of patients. Most of them have high levels of CA 125, except for patients with extraperitoneal recurrence: distant dissemination at lung or brain level [9].

Considering that CA 125 may be normalized after preoperative neoadjuvant chemotherapy (in the advanced stages of the disease), it was found that an increase in its postoperative status is not systematically associated with the suspicion of disease recurrence [10].

Recently, some special laboratory immunological methods have been investigated to detect very low serum concentrations of CA125 in plasma. Specifically, the method consists in isolating anti-CA125 antibodies on the biointerface of graphene-modified nanoparticles with silver nanoparticles (Ag Nps-GQDs). In fact, this could greatly help in the early detection of the disease, and even its recurrence, with prompt treatment [11].

Score ROMA

It is formed by correlating the preoperative CA 125 and HE4 concentrations, depending on the reproductive status of the woman (pre or postmenopausal) and represents a profile for estimating the risk of ovarian cancer. HE4 is the human epididymal protein 4, with strong expression in the cell lines from ovarian tumors and with much lower variability than CA125 in benign conditions. It was approved as a marker in ovarian neoplasm by the FDA in 2008. This algorithm has the main role of calculating the probability of detecting an intraoperative malignant ovarian process.

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Premenopause values: > 11.4% - increased risk of epithelial ovarian cancer

Values of postmenopause: > 29.9% - increased risk of epithelial ovarian cancer detection [12].

Isolated dosage of HE4 in high concentrations in the ascites fluid of patients with ovarian neoplasm represents an adverse prognostic factor in the postoperative evolution of the disease (risk of relapse of the ascites fluid), correlating with an increased resistance to neoadjuvant chemotherapy. Also, the serum dosage as well as the ascites fluid of the two tumor markers, can help to individualize and improve the therapeutic management of the disease [13].

Score Roca

It represents a calculation algorithm, composed of the following criteria: age, reproductive status, risk status (genetic or family history mutations) and serial determinations of CA125. This test has a sensitivity of 85.8% and has been shown to have much greater accuracy of detection, especially for stage I and II disease, compared to single CA 125. Test values: it appreciates the numerical risk and the classification in normal, intermediate and high. In the case of intermediate and high classes, it is recommended to scan the ovaries and repeat the test at 3 months and 6 weeks respectively [14;15].

- Other tumor markers used may also be: CEA, CA 15-3, Alpha-fetoprotein (with overexpression especially in young patients) and Inhibin A (with overexpression especially in tumors of sexual cord cells).

- Given that single dosing of CA125 marker was associated with omission of suspected ovarian neoplasm, a more complex algorithm for dosing multiple tumor markers was proposed, so that the rate of ovarian cancer detection in early stages of disease may increase. Therefore, following a study in which 16 serum biomarkers were tested in 101 ovarian cancer patients and 92 healthy patients, it was found that the dosage of the following biomarkers was associated with a significantly improved disease detection rate: HE4-ELISA, PDGF-AA (Platelet Derived Growth Factor), Prolactin, TTR (Transthyretin) [16].

Transvaginal ultrasound

Combining transvaginal ultrasound with biomarker dosing is the best choice for ovarian cancer screening.

Suspected ultrasound features for neoplasia are: diameter > 8 cm, frequently bilateral, aneural complex mass (solid-hyperechoic, multilocular components with thicknesses > 3 mm with Doppler signal present, calcifications or intrachestatic vegetation), ascites.

Given that some patients are unfortunately evaluated, either by dosing CA125 or by transvaginal ultrasound, it was found that patients who underwent ultrasound examination had suspected ovarian neoplasm had a much worse prognosis than those who had suspected disease based strictly on a modified CA125 [17-22].

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