Taiwanese Journal of Obstetrics & Gynecology 54 (2015) 766–772

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Significance of adding progesterone to the Risk of Ovarian Malignancy Algorithm for early stage ovarian cancer detection in patients with a pelvic mass: A single-center case–control study

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ARTICLE INFO

Article history:
Accepted 11 August 2015

Keywords:
cancer antigen-125
human epididymis protein 4
ovarian cancer
progesterone
ROMA

ABSTRACT

Objective: To evaluate the clinical significance of the combination of cancer antigen-125 (CA-125), human epididymis protein 4 (HE4), and progesterone for the identification of ovarian masses in patients with suspected early stage ovarian cancer (OC).

Materials and methods: This was a case–control, single-center study of 225 women with a pelvic mass of suspected ovarian origin, including 75 patients with Stage I/II OC and 150 controls. Diagnostic procedures included pelvic and rectal examinations, transvaginal ultrasound, evaluation of CA-125 and HE4 levels alone and in the Risk of Ovarian Malignancy Algorithm (ROMA), and a new algorithm combining ROMA and progesterone.

Results: Median CA-125 and HE4 levels were significantly higher in patients with OC compared with women with benign ovarian tumors, irrespective of menopausal status. The highest median progesterone levels occurred in premenopausal women with benign ovarian tumors, compared with premenopausal women with OC with or without benign ovarian disease. The combination of ROMA and progesterone was significantly more accurate at detecting OC compared with ROMA or CA-125 or HE4 alone, but only in premenopausal patients.

Conclusion: Different algorithms should be used for diagnosing OC, and the addition of progesterone might improve the performance of ROMA for the diagnosis of pelvic masses in premenopausal women.

Introduction

Ovarian masses are regularly detected in many women who then undergo evaluations to determine if these masses are malignant. Imaging techniques and laboratory tests can help primary-care physicians and gynecologists to determine the likelihood of cancer and to decide if the patient should be referred to a gynecologic oncologist. Women with ovarian cancer (OC) who are treated by a gynecologic oncologist tend to have better outcomes than those treated by general gynecologists or surgeons [1].

Transvaginal sonography is currently the most widely used diagnostic tool for detecting and differentiating ovarian masses [2,3]. Computed tomography (CT), magnetic resonance imaging, and positron emission tomography can all be used in the determination and diagnosis of an ovarian mass, and all play pivotal roles in the staging, treatment selection, and follow-up of patients with OC [4,5].

In addition to imaging techniques, laboratory tests are also used extensively in the differential diagnosis and therapy follow-up of patients with OC. The first approved OC marker was the cancer antigen-125 (CA-125), which is elevated in approximately 80% of patients with OC. CA-125 has a sensitivity of 50% in women with Stage I disease and up to 90% in patients with more advanced-stage disease [6,7]. This biomarker is particularly accurate among postmenopausal women, in whom the positive predictive value (PPV) reaches 98%, compared with only 49% in premenopausal patients [8]. However, CA-125 is nonspecific and can be elevated under many other conditions, including benign gynecologic etiologies, nongynecologic diseases, and other malignancies, such as breast or endometrial cancers [9,10].

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http://dx.doi.org/10.1016/j.tjog.2015.10.006

The novel tumor marker human epididymis protein 4 (HE4) was recently shown to be a complementary marker to CA-125 for differentiating between benign and malignant diseases in women with an ovarian tumor or pelvic mass [11–13]. HE4 is an 11-kDa protein that is a precursor to the epididymal secretory protein E4, and is overexpressed in OC. Using both CA-125 and HE4 according to the Risk of Ovarian Malignancy Algorithm (ROMA) increased sensitivity and specificity compared with either marker alone [14–16]. At a specificity of 75%, the ROMA cutoff value showed sensitivities of 77–81% for premenopausal women and 90–92% for postmenopausal women [16–20].

However, a panel of complementary biomarkers able to detect early stage OC with satisfactory sensitivity and specificity is still required. Early stage OC can be treated effectively by primary surgery followed by chemotherapy, attaining an 80–90% survival rate, whereas women with advanced disease have much poorer prognoses [21]. Novel biomarkers enabling early stage OC diagnosis will thus markedly improve the clinical treatment of OC.

Evidence suggests that ovarian carcinogenesis is affected by steroid hormones, primarily estrogens, and progesterone. Recent data have indicated that estrogens favor neoplastic transformation within the surface epithelium of the ovary, whereas high progesterone levels seem to protect against the development of OC [22,23].

We therefore determined whether progesterone could act as a subsidiary marker to improve the diagnosis of early stage OC. In this study, we evaluated the clinical significance of ROMA combined with progesterone levels for use as a diagnostic tool to differentiate ovarian masses.

Materials and methods

This single-center case–control study was approved by the Institutional Review Board of Jagiellonian University, Krakow, Poland. All patients provided written informed consent.

Patient population

The primary group comprised 1358 patients diagnosed with a pelvic mass of suspected ovarian origin at the Gynecology and Oncology Department between 2008 and 2012, and who were scheduled for surgical intervention. Exclusion criteria were as follows: (1) OC Stage III/IV, (2) age < 18 years, (3) prior bilateral oophorectomy, (4) pregnancy, (5) history of infertility, (6) chronic liver or (7) renal insufficiency, (8) pulmonary cystic fibrosis or tuberculosis, and (9) hormone treatment. Borderline ovarian tumors were considered cancers according to the International Federation of Gynecology and Obstetrics ovarian tumor classification [24]. Menopause was defined clinically as a lack of menstruation for 12 months or more. Every patient with early stage OC was matched for age, age at menarche, parity, and menopausal status with two control patients diagnosed with benign ovarian masses, identified from among the primary group of patients (Figure 1). Participant allocation was carried out using a computer-generated list of random numbers to select control cases from each group of eligible patients using a block size sequence. After applying the exclusion criteria and randomization, 255 patients were selected for the final analysis.

Diagnostic procedures

After recording their medical histories, all patients underwent bimanual pelvic examination, rectal examination by a gynecologic oncology consultant, and ultrasound imaging to document the presence of an ovarian mass. Ultrasonography was performed using a Voluson 730 Pro equipped with a 6.5-MHz transvaginal probe (General Electric Medical Systems, Kretztechnik, Zipf, Austria). For large tumors, a transabdominal scan was also performed using a 2–5-MHz (transabdominal) transducer (General Electric Medical Systems). Chest X-ray and pelvoabdominal CT scan were performed in selected cases as a part of the preoperative work-up.

Blood analysis

Venous blood samples were analyzed to determine CA-125, HE4, and progesterone levels. Blood samples were centrifuged within 4 hours of collection; serum and plasma were collected and dispensed into multiple 5 cm^3 CryoTubes (Sigma-Aldrich Sp. z.o.o. Poznan, Poland), and all samples were frozen to −80°C. The blood samples were only analyzed if the patient ultimately entered the study. Serum CA-125 concentrations were measured using the Architect CA 125II assay (Abbott Diagnostics, Wiesbaden, Germany) and were expressed as units/milliliter (reference range < 35.0 U/mL). Serum HE4 levels were determined using the Architect HE4 assay (Abbott Diagnostics) and were expressed as picomole/liter (reference range < 90.0 pmol/L). Serum progesterone concentrations in premenopausal patients were determined during the secretory phase of the menstrual cycle (because of irregular periods in some patients, progesterone samples were taken at least 20 days from the last menstrual bleeding) using the AxSYM Progesterone Assay (Abbott Diagnostics) based on microparticle enzyme immunoassay technology, and reported in nanogram/milliliter. In postmenopausal patients, progesterone levels were checked in the same blood sample collected for evaluating CA-125 and HE4 levels. The reference level of serum progesterone in the secretory phase of the menstrual cycle was 5.5–38.0 ng/mL, and the postmenopausal reference range was 0.5–1.0 ng/mL, according to the manufacturer's guidelines. The median time between blood sampling for CA125, HE4, and progesterone and surgery was 17.5 days [interquartile range (IQR) 6.0 days].

ROMA

ROMA is used to assess the risk of epithelial OC in patients with an adnexal mass scheduled for surgical intervention. ROMA classifies patients into low- and high-risk groups for malignant disease using algorithms, as described previously [15,16].

ROMA plus progesterone

We also assessed the risk of OC based on ROMA plus progesterone level. The progesterone concentration was coded as a dichotomous value (i.e., within vs. below normal range). If ROMA indicated a low risk of OC, the patient was described as a low-risk case regardless of the progesterone level. If ROMA indicated a high risk of OC but the progesterone level was within the normal range (premenopausal, 5.5–38.0 ng/mL; postmenopausal, 0.5–1.0 ng/mL), then this case was also coded as having low risk. However, if ROMA indicated a high risk of OC and the progesterone level was below the normal range (i.e., <5.5 ng/mL for premenopausal or <0.5 ng/mL for postmenopausal women), the patient was described as a high-risk case.

Surgical treatment

All patients underwent routine surgical treatment, including laparoscopic ovarian cyst enucleation and laparoscopic unilateral adnexectomy or abdominal hysterectomy with bilateral adnexectomy. In all 75 cases of OC, abdominal hysterectomy with bilateral adnexectomy was followed by a full staging procedure [1,25].