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Original Article

Increased Serum Cancer Antigen-125 Is a Marker for Severity of Deep Endometriosis

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ABSTRACT **Study Objective:** To determine whether cancer antigen-125 (CA-125) levels are increased in women with endometriosis, especially in those with endometriomas (OMAs), deep infiltrating lesions (DIE), and superficial endometriosis (SUP) compared with controls without endometriosis in a large cohort of operated women.

Design: Cross-sectional study (Canadian Task Force classification II-2).

Setting: Tertiary-care university hospital.

Patients: Four hundred six women with histologically proven endometriosis and 279 women without endometriosis.

Interventions: Surgical examination of the abdomino-pelvic cavity.

Measurements and Main Results: Preoperative serum CA-125 antigen levels were evaluated by electrochemoluminescence immunoassay in women with endometriosis and controls. Correlations between serum CA-125 levels and clinical and anatomical characteristics of disease severity were examined. Women with endometriosis displayed higher mean serum CA-125 levels compared with disease-free controls (50.1 ± 62.4 U/mL vs 22.5 ± 25.2 U/mL; $p \leq .001$). CA-125 levels were significantly increased in women with OMA (60.8 ± 63.5 U/mL) and DIE (55.2 ± 68.7 U/mL) compared with women with SUP (23.2 ± 24.5 U/mL) and controls (22.5 ± 25.2 U/mL). There was no difference in CA-125 levels between patients with SUP and controls and between patients with OMA and DIE. CA-125 serum levels were correlated with DIE severity: the mean number of DIE lesions and worst DIE lesion.

Conclusion: Serum CA-125 levels were significantly increased in women with severe forms of endometriosis, OMA, and DIE lesions. In addition, elevated serum Ca-125 levels were associated with more severe and extended DIE lesions. In women with superficial peritoneal lesions, CA-125 levels were not different from women without endometriosis. Journal of Minimally Invasive Gynecology (2014) ■, ■–■

Keywords: Ca-125; Deep infiltrating endometriosis; Endometrioma; Endometriosis

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Pelvic pain [1] and infertility [2] are symptoms related to endometriosis, which is a complex, incompletely understood disease that affects up to 6% to 10% of women in their reproductive years [3]. Endometriosis is a heterogeneous gynecologic condition characterized by the presence of endometrium-like implants (glands and stroma) at an ectopic location outside the uterine cavity [4]. The severity of endometriosis has been classically graded according to

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the territorial extension of the lesions following the I to IV Revised American Fertility Society (rAFS) score [5]. Another classification, which is based on the nature of endometriosis lesions and their degree of invasion of the underlying anatomical structure distinguishes, from the least to the most severe lesion, among peritoneal superficial endometriosis (SUP), ovarian cysts, endometriomas (OMAs), and deeply infiltrating endometriosis (DIE) [6,7].

Establishing an accurate diagnosis of endometriosis is often problematic because its symptoms (pain and infertility) are nonspecific and can be related to a wide number of different conditions [3,8,9]. To date, there is no noninvasive diagnostic technique available to accurately identify the extension of peritoneal lesions [10,11]. Underestimation of the DIE extension before surgery is 1 main reason that explains why surgery is often incomplete [12] and leads to recurrence of pain symptoms and repeat operative procedures [13–15]. There is currently a need for biomarkers of severe forms of the disease (e.g., DIE) [15]. An elevation of such a biomarker should lead to a thorough preoperative assessment through pelvic imaging to detect and localize deep infiltrating nodules [14]. The evaluation of the nature and extension of endometriosis lesions preoperatively is essential for several reasons: (1) patient informed consent about the severity of the disease and the planned surgical intervention is required; (2) the surgical intervention needs to be complete; and (3) the surgical procedure should be performed by a surgeon who specializes in endometriosis surgery in case of severe DIE.

More than 100 biomarkers and associations of biomarkers have been investigated in relation to the pathogenesis and as putative markers of the severity of the disease [16]. Cancer antigen (CA-125), a glycoprotein, is the biomarker most consistently studied in endometriosis [16]. Recently, European Society of Human Reproduction and Embryology guidelines have stated that CA-125 measurement has limited potential for the diagnose of endometriosis [17]. However, the authors discussed the need of future studies to better evaluate the potential of CA-125 in women with endometriosis, including disease staging and identifying subgroups of patients [17]. Endometriosis is classically assessed by the surgical rAFS classification; however, this classification encompasses a mixture of different anatomical localizations and histological phenotypes of endometriosis, including SUP, OMA, and DIE. Because of disease heterogeneity, CA-125 should be assessed in relation to these different endometriosis surgical categories.

The aim of the present study is to assess preoperative serum CA-125 levels in a large cohort of women according to their histologic phenotype of endometriotic lesions (SUP, OMA, and DIE) and in surgically investigated control patients without endometriosis. Our secondary objective is to evaluate the association of CA-125 with respect to the severity of preoperative symptoms, the type of endometriosis, and the anatomical distribution of DIE lesions.

Methods

Study Subjects

The local ethics committee (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale) of the Cochin University Hospital in Paris approved the study protocol, and all included patients signed a written informed consent form.

Beginning in January 2005, we prospectively collected clinical and biological data in all nonpregnant patients who were younger than 42 years old who were surgically explored for benign gynecologic conditions at our institution. Serum samples were collected before surgery and stored frozen for future analysis. Women with cancers and women who did not consent were excluded from the study. Data were collected in face-to-face interviews for each patient, conducted by the surgeon during the month preceding surgery; we used a structured, previously published questionnaire for these interviews [18]. Briefly, for all patients, we collected general information, including age, gravidity, parity, height, weight, body mass index (BMI), age of menarche, existence and duration of infertility, lifestyle habits, and use of hormonal treatments. We also recorded data concerning the history of hormonal and/or surgical treatments for treating symptomatic endometriosis and the existence of gynecologic pain symptoms (dysmenorrhea, deep dyspareunia, or noncyclic chronic pelvic pain [NCCPP]), as well as gastrointestinal and lower urinary tract symptoms. NCCPP is defined as intermittent or permanent pelvic pain that is not related to the menstrual cycle [19]. Gastrointestinal symptoms, which are often nonspecific, are most typically seen as painful defecation or constipation that worsens in the menstrual period [20]. Lower urinary tract symptoms were defined as 1 or more of the following symptoms, either chronic or during menstruation: hematuria, nonmicrobial cystitis, recurrent urinary tract infections, pain on urinating, pollakiuria, and dysuria [18]. The pain intensity was evaluated preoperatively using a 10-cm visual analog scale [21].

As described in the study flowchart (Fig. 1), 1439 women underwent surgery, of whom 1306 signed the informed consent form. Of 798 women with a surgical visual diagnosis of endometriosis, 691 had histologically proven endometriosis. Frozen serum samples for CA-125 measurement and completed clinical questionnaires were available for 406 women (study group). Of the 508 women without visual endometriosis, 279 had frozen serum samples for CA-125 measurement and completed clinical questionnaires; these women constituted the control group. Women were classified in 2 groups according to the surgical findings. The endometriosis group (n = 406) consisted of patients with surgically and histologically proven endometriosis, and the control group (n = 279) consisted of women without any macroscopic visual endometriosis lesion, as confirmed after a thorough examination of the abdomino-pelvic cavity during surgery. Among control group women, the indications