ORIGINAL PAPER

RJME Romanian Journal of Morphology & Embryology http://www.rjme.ro/

The added value of CA125, HE4, and CA72-4 as markers for ovarian endometriosis diagnosis

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Abstract

Objective: This study aimed to evaluate the prognostic value as diagnosis makers of cancer antigen (CA)125, human epididymis 4 (HE4), and CA72-4 serum levels in ovarian endometriosis (OvEndo). *Patients, Materials and Methods*: The serum levels of CA125, HE4, and CA72-4 were measured using enzyme-linked immunosorbent assay (ELISA) technique for a group of 29 cases of OvEndo and a control (CTR) group of 26 cases. *Results*: Results were compared between groups and statistical correlation was analyzed between the three biomarkers. (*i*) For CA125, we found a statistically significant difference in-between the mean serum levels of the two groups: 9.02 U/mL in the OvEndo group *versus* 7.1 U/mL in the CTR group (p=0.0158). (*ii*) A similar situation was found for CA72-4 levels in OvEndo group, where the mean serum level was 6.1 U/mL compared to 3.5 U/mL in the CTR group, showing a significant difference (p=0.0185). (*iii*) The mean serum level of HE4 in the OvEndo group was 7.6 ng/mL *versus* 7.8 ng/mL in the CTR group, and we found it highly significant (p=0.0001). HE4 levels were highly correlated with CA72-4 levels (p<0.0001), while CA125 levels were not correlated with HE4 and CA72-4. *Conclusions*: Measurements of CA125 can be used in the diagnosis of OvEndo mainly in association with HE4 serum levels, which are lower in endometriosis patients. CA72-4 levels are highly correlated with HE4 levels in patients with OvEndo, while no correlation with the other two markers was found. This correlation needs further investigation to establish if it may be used as a possible diagnostic tool in clinical practice.

Keywords: CA125, HE4, CA72-4, ovarian endometriosis, prognostic.

Introduction

Endometriosis is a gynecological pathology that affects 10–15% of all reproductive-age women [1]. Ovarian endometriosis (OvEndo) or endometrioma is the most common subtype and affects 17–44% of women with endometriosis. Through the mass effect exercised on ovarian parenchyma the endometrioma can significantly reduce the functional ovarian tissue [2]. Bowel involvement by deep endometriosis constitutes a difficult task for the gynecologist and has been estimated to occur in 8–12% of patients with endometriosis [3]. Recto-sigmoid localization occupies 80–90% of the forms of digestive endometriosis [4].

With all the great achievements in the medical imagistic field, diagnosing endometriosis is still a difficult task for health practitioners. Even the recommended standard technique, laparoscopy, has some downsides as it is an invasive procedure at high expense. Moreover, it is not very helpful in diagnosis of retroperitoneal and deep infiltrating lesions. Consequently, many researchers are highly motivated to explore cost-effective and non-invasive biomarkers for identifying patients with suspected endometriosis.

Differentiating between OvEndo, other benign ovarian tumors and early malignant ovarian tumors is a mandatory first step when an ovarian mass is discovered. Moreover, early detection and therapeutic follow-up represent a target in the management of endometriosis.

Non-invasive biological biomarkers represent an important direction for research in this pathology, but one single marker is not sufficient for the diagnosis of endometriosis. Therefore, the use of a combination of cancer antigen (CA)125, human epididymis 4 (HE4), and CA72-4 markers is more promising.

CA125 is a large membrane glycoprotein known also as mucin-type glycoprotein (MUC16). *MUC16* gene belongs to the mucin family and secretes proteins named mucins, which are heavily glycosylated. *MUC16* gene encodes CA125 protein [5, 6]. The biomarker is most often used for ovarian lesions but, also, one of the most important markers in the diagnosis and follow-up of endometriosis. Several studies demonstrated that serum CA125 concentrations are elevated in patients with OvEndo [7–10].

HE4, nominated in the literature as WAP four-disulfide core domain protein 2 (WFDC2), was initially identified in epithelial cells of the human epididymis [11]. HE4 immunoreactivity is highest in the glandular epithelium of the genital tract, including endocervical glands, endometrial glands, Fallopian tubes, and Bartholin's glands. Regarding the ovary, cortical inclusion cysts arising here express this

protein abundantly [12]. Galgano *et al.* concluded that the gene responsible for the coding of HE4 is not overexpressed in endometriotic lesions [13].

CA72-4 is an antigenic determinant of the tumor-associated glycoprotein-72 (TAG-72). *TAG-72* is the gene that encodes the CA72-4 molecule [14]. This antigen was mentioned in a variety of human adenocarcinomas, such as ovarian, breast, colorectal, gastric and lung, while in normal and benign tissue is rarely expressed [15–17]. The impact and utility of CA72-4 in the pathology of endometriosis are not well known.

Aim

The present study measured the serum levels of CA125, HE4, and CA72-4 markers in patients with OvEndo. The data were compared with control (CTR) patients without endometriosis to evaluate the prognostic value of these serological markers.

Patients, Materials and Methods

Patients

From the patients enrolled in this study, those known with OvEndo were treated in Emergency County Hospital, Cluj-Napoca, Romania, and the CTR group was structured from selected patients of the Regional Transfusion Center, Cluj-Napoca. All patients filled in a written informed consent sampling. The procedures followed all the ethical standards. The Ethics Committee of Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, consented to this Decision with No. 74/16.02.2015. The main symptoms mentioned by the patients enrolled in the study were pelvic pain, dyspareunia, dysuria, dyskinesia, vaginal bleeding. For those patients who did not present any symptoms, diagnostic has been performed by ultrasonographic methods. The mean age was 30 years, and more than half of the cases diagnosed with OvEndo presented deep endometriosis also. Of a total of 55 patients enrolled, 29 had OvEndo and 26 were CTRs. The surgical diagnosis was performed by laparoscopy/laparotomy, and all were subsequently validated by histopathological (HP) results.

Serum CA125, HE4, and CA72-4 analyses

Blood samples collection was performed before each surgery in non-heparinized tubes and centrifugated at 4000 rpm. The serum samples obtained were analyzed according to enzyme-linked immunosorbent assay (ELISA) manufacturer's instruction to evaluate CA125, HE4, and CA72-4 levels. The kits used were Human CA125 ELISA kit (Elabscience), Human HE4 ELISA kit (Wuhan Fine BioTech), and Human CA72-4 ELISA kit (ANOVA) (Figure 1).

For CA125, a value greater than 35 U/mL has been settled as a positive variable in the screening of epithelial ovarian cancer [18]. For endometriosis instead, a decisive cutoff value has not been set yet. For CA72-4, cutoff value was targeted to 3.8 U/mL [19], and the HE4 value of 46 pM [8] corresponding to 20.4 ng/mL was considered as a cut-off. The results were analyzed with GraphPad Prism 6, p-value <0.05 was considered statistically significant. The Spearman's correlation coefficient (r) was defined as a value between -1 and 1, with a linear regression line of a 95% confidence interval (CI). The reference value for the area under the receiver operating characteristic (ROC) curve (AUC) was reported to 1.

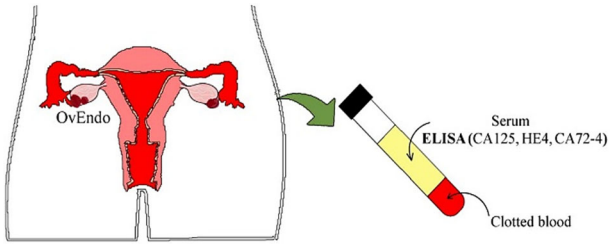

Figure 1 – ***Serum CA125, HE4, and CA72-4 ELISA analyses in patients with OvEndo and CTR. Blood samples were collected from each patient group included in the study, OvEndo and CTR, in non-heparinized tubes and centrifugated. Serum samples concentrations were performed for each marker, CA125, HE4, and CA72-4. CA: Cancer antigen; CTR: Control; ELISA: Enzyme-linked immunosorbent assay; HE4: Human epididymis 4; OvEndo: Ovarian endometriosis.***

Results

Most patients with OvEndo (58%) were under the age of 30 years (mean 30.1 years, range 20–48 years). More than half of the patients with OvEndo associated deep endometriosis (15 cases, representing 51.7%) and, besides pelvic pain, these patients also presented dyspareunia, dysuria, and dyskinesia.

Demographic and clinical parameters of the patients are included in Table 1.

Table 1 – ***Clinical parameters in OvEndo***

Clinical parameters	OvEndo, *n*=29 (%)
Symptoms	
▪ Pelvic pain	27 (66%)
▪ Dyspareunia	2 (5%)
▪ Dysuria	1 (2.5%)
▪ Dyskinesia	3 (7%)
▪ Vaginal bleeding	7 (17%)
▪ No symptoms	1 (2.5%)
Age [years]	
▪ <30	17
▪ 30–39	10
▪ 40	2
▪ Mean	30.1
▪ Range	20–48
Deep endometriosis association	15 (51.7%)

n: No. of cases; OvEndo: Ovarian endometriosis.

From a histological point of view, the elements which define endometriosis are represented by the endometrial-type glands, simple or sometimes atypical ones, and endometrial stroma, which may contain hemosiderin deposits, inflammatory infiltrate (neutrophils, eosinophils, lymphocytes), blood vessels and active hemorrhage [18] (Figure 2, A–D).

The first serological marker analyzed was CA125. In OvEndo cases, the mean serum level was 13.1 U/ml ± 14.4 standard deviation (SD) (median 9.02 U/mL). In CTR patients, mean serum level was 7.1 U/ml ± 3.6 SD (median 5.3 U/mL) (Table 2).

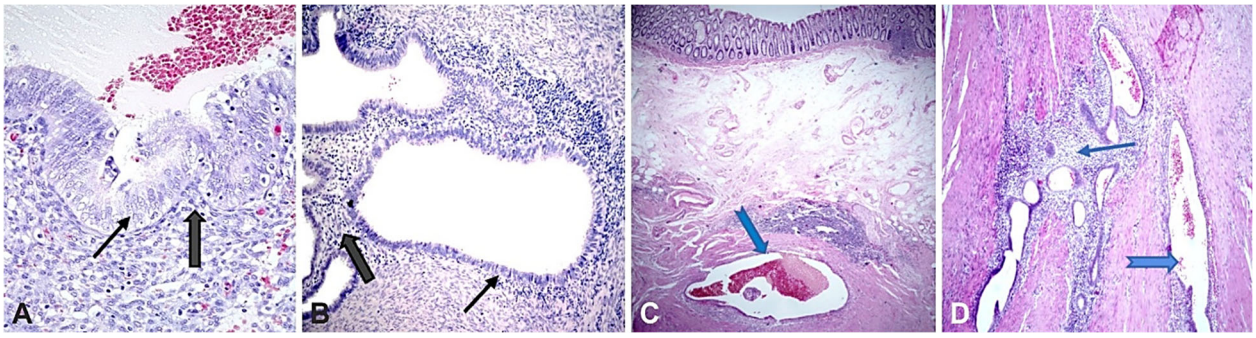

Figure 2 – *Microscopic examination of endometriosis involvement: (A and B) Ovarian endometriosis – endometrial stroma (thick arrow), endometrial gland (thin arrow); (C and D) Colorectal endometriosis – endometrial gland (thick bule arrow) without mucosal involvement, endometrial gland (thick blue arrow), stroma inflammatory infiltrate located in the muscle layer (thin blue arrow). Hematoxylin–Eosin (HE) staining: (A and D) ×100; (B) ×200; (C) ×40.*

HE4 in OvEndo group had a mean serum level of 7.6 ng/mL ± 6.6 SD (median 6.5 ng/mL), while in the CTR group, mean serum level was 7.8 ng/mL ± 0.8 SD (median 7.4 ng/mL). For CA72-4 in OvEndo, the mean serum level was 6.1 U/mL ± 4.7 SD (median 4.9 U/mL), and in the CTR group, mean serum level was 3.5 U/mL ± 2.2 SD (median 2.4 U/mL) (Table 2).

Comparing OvEndo *versus* CTR for CA125 levels, the p=0.0158 pointed out a significant statistical difference, while for HE4, a p-value of 0.0001 was highly significant. Similar, for the CA72-4 levels, the p=0.0185 was statistically significant. The AUC in the OvEndo group was 0.78 for both CA72-4 and HE4 serum markers and 0.65 for CA125 (Figure 3, A–F).

Table 2 – *Serum CA125, HE4, and CA72-4 levels in CTRs and OvEndo patients*

		Mean	Median	SD	Range	*p*-value
CA125 [U/mL]	CTR	7.1	5.3	3.6	3.2–16.6	
	OvEndo	13.1	9.02	14.4	3.5–73.2	0.0158[a]
HE4 [ng/mL]	CTR	7.8	7.4	0.8	6.4–9.4	
	OvEndo	7.6	6.5	6.6	4.8–42.8	<0.0001[a]
CA72-4 [U/mL]	CTR	3.5	2.4	2.2	1.8–9.3	
	OvEndo	6.1	4.9	4.7	2.7–25.2	0.0185[a]

CA: Cancer antigen; CTR: Control; HE4: Human epididymis 4; OvEndo: Ovarian endometriosis; SD: Standard deviation. [a]*p*-value comparing OvEndo group with CTR group.

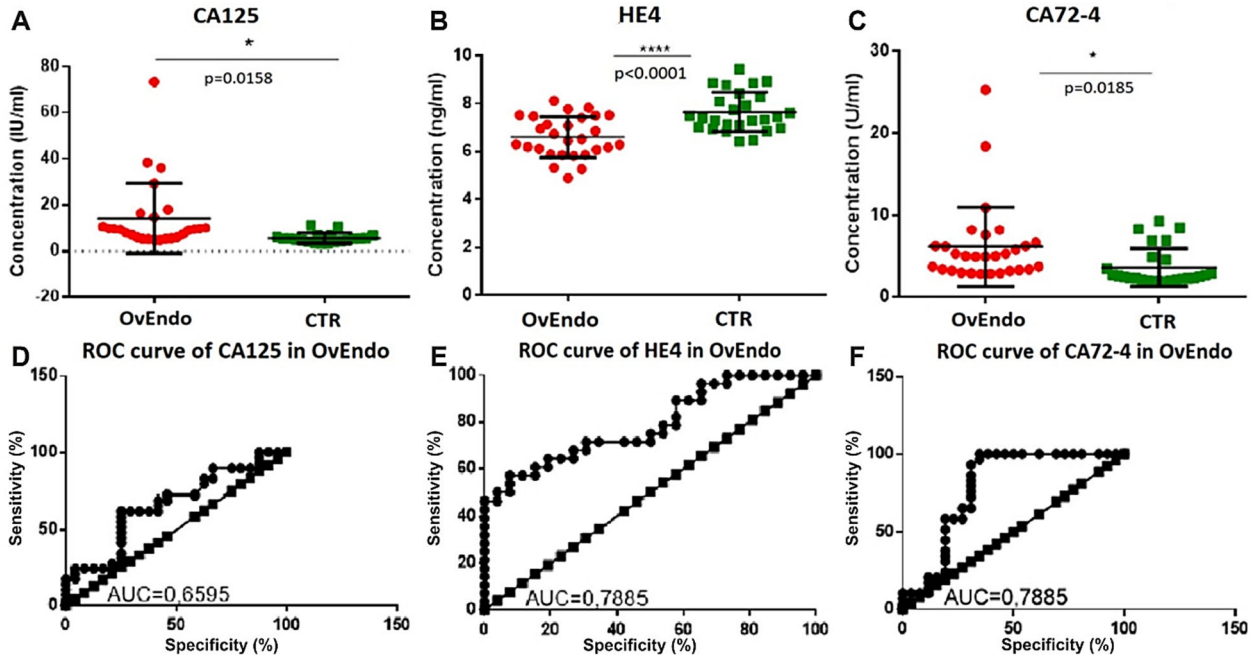

Figure 3 – *(A–F) Expression levels of CA125, HE4, and CA72-4 serum markers in CTRs and OvEndo. AUC: Area under the curve; CA: Cancer antigen; CTR: Control; HE4: Human epididymis 4; OvEndo: Ovarian endometriosis; ROC: Receiver operating characteristic.*

First line graphs highlight the representation of the expression levels in selected groups. The scatter dots plots describe the serum levels of CA125, HE4 and CA72-4 markers for each OvEndo and CTR group. Lines represent the means and limits of the 95% CI. *P*-values between CTR–OvEndo were calculated with a non-parametric *t*-test. In the OvEndo group, significantly serum levels of all three tested markers were obtained. The second line graphs represent the ROC curve for CA125, HE4, and CA72-4 markers in endometriosis. The AUC and the ROC curve in the OvEndo group evaluated a positive predictive value for CA125, HE4, and CA72-4 markers.

Correlation of CA125, HE4, and CA72-4 serum levels in selected groups

Linear regression line, Spearman's correlation coefficient (r), and p-value were determined for all three markers in OvEndo and CTR groups (Figure 4, A–F).

Spearman's correlation coefficient, defined as a value between -1 and 1, quantifies the strength of binomial association between the CA125, HE4, and CA72-4 markers in CTR and OvEndo groups.

In the CTR group, there was no correlation between the serum markers, each p-value being framed as >0.05 statistically not significant and Spearman's correlation coefficients suggested a very weak association: between CA125 and CA72-4, the p-value was 0.47 and r=0.01; between HE4 and CA72-4, the p-value was 0.32 and r=0.09; between HE4 and CA125, the p-value was 0.1 and r=0.26.

In the OvEndo group, the statistical correlation between HE4 and CA72-4 showed a p<0.0001 highly significant and r=0.74 suggestive for a highly positive association. Going further, between CA125–CA72-4 and HE4–CA125 were highlighted a statistically not significant p-value of 0.18 and 0.1, respectively, and r=0.17 and 0.18 concluded a weak association.

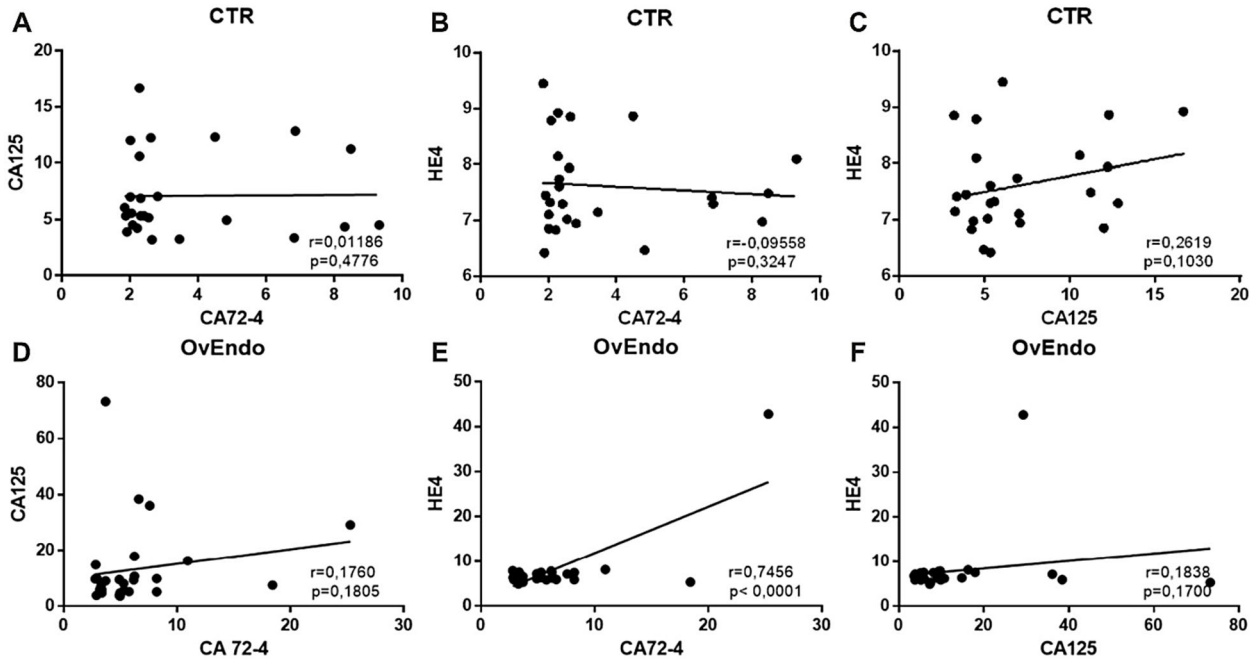

Figure 4 – ***(A–F) Linear regression and Spearman's rank correlation analyses between the determined serum markers. CA: Cancer antigen; CTR: Control; HE4: Human epididymis 4; OvEndo: Ovarian endometriosis.***

Discussions

Endometriosis is known to be a gynecological condition with a high incidence among young patients and its prevalence worldwide has been steadily rising, approaching nearly 15%, probably because menarche occurs much earlier nowadays compared to few decades ago [19]. The defining feature of endometriosis involves the migration of cells resembling those of the endometrium to ectopic locations beyond the anatomical limits of the uterus.

The most frequent complaints of patients with endometriosis are chronic pelvic pain, dysmenorrhea, and infertility, but conversely 20–25% of patients remain asymptomatic [20]. Infertility is expected to be found in 30–50% of patients with endometriosis. Due to the low specificity of these symptom clusters that can also resemble pelvic inflammatory disease or other conditions linked to chronic pelvic pain, surgical procedures coupled with HP examinations are considered to be the "gold standard" for establishing a conclusive diagnosis [21]. Due to the invasiveness of the procedure, which is a major drawback, and the long-time frame from performing the procedure and the final HP result, many research studies tried to identify biological noninvasive markers for early diagnosis, like CA125, CA199, urocortin or interleukin-6 (IL-6) [22–24].

However, all these emerging indicators, despite the promising results, are far from meeting the criteria for diagnostic biomarkers used alone and their association seems to be more successful [25].

The target of this study was to evaluate the clinical utility and importance of CA125, HE4 and CA72-4 serological markers and their association, in differentiating OvEndo from CTR.

The CA125 serum levels in patients with OvEndo (mean 13.2 U/mL, median 9.02 U/mL, range 3.5–73.2 U/mL) were higher statistically significant compared to CTR (mean 7.3 U/mL, median 5.4 U/mL, range 3.2–16.6 U/mL). In the literature, for CA125 marker, Liu *et al.* reported median values in OvEndo (84.9 kU/L) and in healthy women (11.5 kU/L) [26]. Dong *et al.* presented a median value for endometriotic diseases (53 kU/L), which was higher than that in a healthy women group (11 kU/L) and mentioned it was statistically significant (p=0.031) [27].

The HE4 serum levels in patients with OvEndo (mean 7.6 ng/mL, corresponding to 17.5 pM; median 6.5 ng/mL, corresponding to 14.6 pM, range 4.8–42.8 ng/mL) compared to CTR (mean 7.8 ng/mL, corresponding to 17.07 pM; median 7.4 ng/mL, corresponding to 16.6 pM, range 6.4–9.5 ng/mL) highlighted similar values and the p=0.0001

was highly significant. Other studies also mentioned that serum levels of HE4, in patients with OvEndo, were not affected by this pathology [7–10]. Compared to healthy subjects, the HE4 levels did not reveal significant changes (p=0.128 and p=0.27, respectively) [7, 8]. Huhtinen *et al.* presented in patients with OvEndo (46.0 pM) a mean value comparable with healthy CTRs (40.5 pM) [7, 8]. Chen *et al.* obtained a median (53.0 pM) in patients with endometrioma [10]. Liu *et al.* concluded median levels of HE4 for endometriosis (52.4 pM) and for CTR (50.0 pM), which did not show statistical difference [26].

The CA72-4 serum levels in patients with OvEndo (mean 6.1 U/mL, median 4.9 U/mL, range 2.7–25.2 U/mL) compared to CTR (mean 3.5 U/mL, median 2.4 U/mL, range 1.8–9.3 U/mL) highlighted higher values and p=0.0185 was significant. Anastasi *et al.* presented for CA72-4 in OvEndo a mean value of 3.1 U/mL, a median of 2.7 U/mL, where the range was 1.8–10 U/mL [28]. Chen *et al.* obtained a value of 1.7 U/mL for median in benign ovarian diseases [10].

In the OvEndo group, correlation between CA125 and HE4 suggested a weak association with Spearman's coefficient r=0.18, compared with Huhtinen *et al.*, which observed a more accurate diagnostic tool [7]. The linear regression highlighted a strong correlation between HE4 and CA72-4, where p<0.0001 and r=0.74.

In the OvEndo group, the mean age was 30 years. A correlation between age and serum levels for CA125, HE4, and CA72-4 markers in this group could not be established. In literature, Karimi-Zarchi *et al.* did not observe any correlation between age and CA125 in OvEndo (p=0.76) [29]. Hallamaa *et al.* presented no correlation between age and HE4 or CA125 [30]. Regarding the age of the manifestation of this pathology, the mean of 30 years is the age of maximum reproduction period and OvEndo can compromise the ovarian reserve. For this reason, the management of fertility and the cryopreservation of the oocytes or ovarian tissue must be considered [31].

Conclusions

Measurements of CA125 serum concentration can be used in the diagnosis of OvEndo as CA125 serum levels were higher in patients with OvEndo compared to CTR. HE4 serum levels were lower in patients with OvEndo and highly correlated with CA72-4 levels, making this association a possible diagnostic tool to be further investigated. OvEndo can be considered if the levels of CA125 marker are elevated while HE4 levels decrease.

Conflict of interests

The authors have declared no conflict of interests.

Acknowledgments

This manuscript was sustained by the Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania, for PhD research projects No. 7690/46/15.04.2016 and No. 5200/41/01.03.2017.

Authors' contribution

Romeo Micu and Adriana Maria Ioana Gaia-Oltean have equal contributions to this study.

References

[1] Giudice LC, Kao LC. Endometriosis. Lancet, 2004, 364(9447): 1789–1799. https://doi.org/10.1016/S0140-6736(04)17403-5 PMID: 15541453

[2] Alkatout İ, Meinhold-Heerlein I, Keckstein J, Mettler L. Endometriosis: a concise practical guide to current diagnosis and treatment. J Turk Ger Gynecol Assoc, 2018, 19(3):173–175. https://doi.org/10.4274/jtgga.2018.0026 PMID: 29755027 PMCID: PMC6085527

[3] Abrão MS, Petraglia F, Falcone T, Keckstein J, Osuga Y, Chapron C. Deep endometriosis infiltrating the recto-sigmoid: critical factors to consider before management. Hum Reprod Update, 2015, 21(3):329–339. https://doi.org/10.1093/humupd/dmv003 PMID: 25618908

[4] Doh K, Thiam I, Ka S, Dial C, Woto-Gaye G. [Rectal endometriosis: an exceptional etiology of acute intestinal occlusion]. Ann Pathol, 2016, 36(6):412–414. https://doi.org/10.1016/j.annpat.2015.11.014 PMID: 27079729

[5] Bottoni P, Scatena R. The role of CA 125 as tumor marker: biochemical and clinical aspects. Adv Exp Med Biol, 2015, 867:229–244. https://doi.org/10.1007/978-94-017-7215-0_14 PMID: 26530369

[6] McLemore MR, Aouizerat B. Introducing the *MUC16* gene: implications for prevention and early detection in epithelial ovarian cancer. Biol Res Nurs, 2005, 6(4):262–267. https://doi.org/10.1177/1099800404274445 PMID: 15788735

[7] Huhtinen K, Suvitie P, Hiissa J, Junnila J, Huvila J, Kujari H, Setälä M, Härkki P, Jalkanen J, Fraser J, Mäkinen J, Auranen A, Poutanen M, Perheentupa A. Serum HE4 concentration differentiates malignant ovarian tumours from ovarian endometriotic cysts. Br J Cancer, 2009, 100(8):1315–1319. https://doi.org/10.1038/sj.bjc.6605011 PMID: 19337252 PMCID: PMC2676558

[8] Shin KH, Kim HH, Kwon BS, Suh DS, Joo JK, Kim KH. Clinical usefulness of cancer antigen (CA) 125, human epididymis 4, and CA72-4 levels and risk of ovarian malignancy algorithm values for diagnosing ovarian tumors in Korean patients with and without endometriosis. Ann Lab Med, 2020, 40(1):40–47. https://doi.org/10.3343/alm.2020.40.1.40 PMID: 31432638 PMCID: PMC6713655

[9] Terry KL, Sluss PM, Skates SJ, Mok SC, Ye B, Vitonis AF, Cramer DW. Blood and urine markers for ovarian cancer: a comprehensive review. Dis Markers, 2004, 20(2):53–70. https://doi.org/10.1155/2004/241982 PMID: 15322314 PMCID: PMC3839278

[10] Chen X, Zhou H, Chen R, He J, Wang Y, Huang L, Sun L, Duan C, Luo X, Yan H. Development of a multimarker assay for differential diagnosis of benign and malignant pelvic masses. Clin Chim Acta, 2015, 440:57–63. https://doi.org/10.1016/j.cca.2014.11.013 PMID: 25447698

[11] Hellström I, Raycraft J, Hayden-Ledbetter M, Ledbetter JA, Schummer M, McIntosh M, Drescher C, Urban N, Hellström KE. The HE4 (WFDC2) protein is a biomarker for ovarian carcinoma. Cancer Res, 2003, 63(13):3695–3700. PMID: 12839961

[12] Drapkin R, von Horsten HH, Lin Y, Mok SC, Crum CP, Welch WR, Hecht JL. Human epididymis protein 4 (HE4) is a secreted glycoprotein that is overexpressed by serous and endometrioid ovarian carcinomas. Cancer Res, 2005, 65(6):2162–2169. https://doi.org/10.1158/0008-5472.CAN-04-3924 PMID: 15781627

[13] Galgano MT, Hampton GM, Frierson HF Jr. Comprehensive analysis of HE4 expression in normal and malignant human tissues. Mod Pathol, 2006, 19(6):847–853. https://doi.org/10.1038/modpathol.3800612 PMID: 16607372

[14] Sheer DG, Schlom J, Cooper HL. Purification and composition of the human tumor-associated glycoprotein (TAG-72) defined by monoclonal antibodies CC49 and B72.3. Cancer Res, 1988, 48(23):6811–6818. PMID: 3180090

[15] Thor A, Ohuchi N, Szpak CA, Johnston WW, Schlom J. Distribution of oncofetal antigen tumor-associated glycoprotein-72 defined by monoclonal antibody B72.3. Cancer Res, 1986, 46(6):3118–3124. PMID: 3516392

[16] Nuti M, Teramoto YA, Mariani-Costantini R, Hand PH, Colcher D, Schlom J. A monoclonal antibody (B72.3) defines patterns of distribution of a novel tumor-associated antigen in human mammary carcinoma cell populations. Int J Cancer, 1982, 29(5):539–545. https://doi.org/10.1002/ijc.2910290509 PMID: 6284656

[17] Bast RC Jr, Klug TL, St John E, Jenison E, Niloff JM, Lazarus H, Berkowitz RS, Leavitt T, Griffiths CT, Parker L, Zurawski VR Jr, Knapp RC. A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. N Engl J Med, 1983, 309(15):883–887. https://doi.org/10.1056/NEJM198310133091503 PMID: 6310399

[18] Worley MJ, Welch WR, Berkowitz RS, Ng SW. Endometriosis-associated ovarian cancer: a review of pathogenesis. Int J Mol Sci, 2013, 14(3):5367–5379. https://doi.org/10.3390/ijms14035367 PMID: 23466883 PMCID: PMC3634491

[19] Moga MA, Bălan A, Dimienescu OG, Burtea V, Dragomir RM, Anastasiu CV. Circulating miRNAs as biomarkers for endometriosis and endometriosis-related ovarian cancer – an overview. J Clin Med, 2019, 8(5):735. https://doi.org/10.3390/jcm8050735 PMID: 31126056 PMCID: PMC6571871

[20] Bulletti C, Coccia ME, Battistoni S, Borini A. Endometriosis and infertility. J Assist Reprod Genet, 2010, 27(8):441–447. https://doi.org/10.1007/s10815-010-9436-1 PMID: 20574791 PMCID: PMC2941592

[21] Agarwal SK, Chapron C, Giudice LC, Laufer MR, Leyland N, Missmer SA, Singh SS, Taylor HS. Clinical diagnosis of endometriosis: a call to action Am J Obstet Gynecol, 2019, 220(4): 354.e1–354.e12. https://doi.org/10.1016/j.ajog.2018.12.039 PMID: 30625295

[22] Laganà AS, Vitale SG, Salmeri FM, Triolo O, Ban Frangež H, Vrtačnik-Bokal E, Stojanovska L, Apostolopoulos V, Granese R, Sofo S. *Unus pro omnibus*, *omnes pro uno*: a novel, evidence-based, unifying theory for the pathogenesis of endometriosis. Med Hypotheses, 2017, 103:10–20. https://doi.org/10.1016/j.mehy.2017.03.032 PMID: 28571791

[23] Vitale SG, Capriglione S, Peterlunger I, La Rosa VL, Vitagliano A, Noventa M, Valenti G, Sapia F, Angioli R, Lopez S, Sarpietro G, Rossetti D, Zito G. The role of oxidative stress and membrane transport systems during endometriosis: a fresh look at a busy corner. Oxid Med Cell Longev, 2018, 2018: 7924021. https://doi.org/10.1155/2018/7924021 PMID: 29743986 PMCID: PMC5883985

[24] Chen Y, Zhu HL, Tang ZW, Neoh KH, Ouyang DF, Cui H, Cheng HY, Ma RQ, Ye X, Han RP, Chang XH. Evaluation of circulating endometrial cells as a biomarker for endometriosis. Chin Med J (Engl), 2017, 130(19):2339–2345. https://doi.org/10.4103/0366-6999.215325 PMID: 28937041 PMCID: PMC5634086

[25] Anastasi E, Granato T, Falzarano R, Storelli P, Ticino A, Frati L, Panici PB, Porpora MG. The use of HE4, CA125 and CA72-4 biomarkers for differential diagnosis between ovarian endometrioma and epithelial ovarian cancer. J Ovarian Res, 2013, 6(1):44. https://doi.org/10.1186/1757-2215-6-44 PMID: 23816286 PMCID: PMC3701500

[26] Liu YN, Ye X, Cheng HY, Cheng YX, Fu TY, Chen J, Chang XH, Cui H. [Measurement of serum human epididymis secretory protein 4 combined with CA125 assay in differential diagnosis of endometriosis cyst and ovarian benign and malignant tumors]. Zhonghua Fu Chan Ke Za Zhi, 2010, 45(5):363–366. PMID: 20646446

[27] Dong L, Chang XH, Ye X, Zhu LR, Zhao Y, Tian L, Cheng HY, Li XP, Zhang H, Liao QP, Fu TY, Cheng YX, Cui H. [The values of serum human epididymis secretory protein 4 and CA(125) assay in the diagnosis of ovarian malignancy]. Zhonghua Fu Chan Ke Za Zhi, 2008, 43(12):931–936. PMID: 19134334

[28] Anastasi E, Manganaro L, Granato T, Benedetti Panici P, Frati L, Porpora MG. Is CA72-4 a useful biomarker in differential diagnosis between ovarian endometrioma and epithelial ovarian cancer? Dis Markers, 2013, 35(5):331–335. https://doi.org/10.1155/2013/984641 PMID: 24191126 PMCID: PMC3793285

[29] Karimi-Zarchi M, Dehshiri-Zadeh N, Sekhavat L, Nosouhi F. Correlation of CA-125 serum level and clinico-pathological characteristic of patients with endometriosis. Int J Reprod Biomed, 2016, 14(11):713–718. PMID: 28008424 PMCID: PMC5153578

[30] Hallamaa M, Suvitie P, Huhtinen K, Matomäki J, Poutanen M, Perheentupa A. Serum HE4 concentration is not dependent on menstrual cycle or hormonal treatment among endometriosis patients and healthy premenopausal women. Gynecol Oncol, 2012, 125(3):667–672. https://doi.org/10.1016/j.ygyno.2012.03.011 PMID: 22426487

[31] Micu R, Petrut B, Zlatescu-Marton C, Traila A, Harsa R, Achimas-Cadariu P. Current strategies and future perspectives in fertility preservation for cancer patients. J BUON, 2017, 22(4):844–852. PMID: 29155509

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Received: April 18, 2023

Accepted: June 23, 2023