Is inhibin a useful serum marker for postmenopausal women with epithelial ovarian cancer?

Abstract

Ovarian cancer is one of the most common causes of death in women, and epithelial ovarian cancer is the most frequent type. It is often diagnosed in an advanced clinical stage (stage III or IV) and the long-term survival rate is low. One of the reasons is that the available diagnostic tests are limited by their sensitivity and specificity characteristics. The early detection of ovarian cancer is the key to reduce the mortality and morbidity. It is known that CA 125 is used for the diagnosis and follow-up of epithelial ovarian cancer, and inhibin is a sensitive marker for mucinous and granulosa-cell tumors of the ovary. But there are some studies which suggest that serum inhibin is also elevated in some postmenopausal women with epithelial ovarian tumors. Inhibin is an ovarian hormone involved in the regulation of fertility, decreasing to undetectable levels at menopause. Its increase in postmenopausal women with epithelial ovarian cancer led to a series of studies which evaluated the possibility of inhibin being a serum marker for epithelial ovarian cancer. Despite the numerous reviews, the exact role of inhibin in epithelial ovarian cancer has not been established yet. It is accepted that combinations of biomarkers may improve ovarian cancer detection. Inhibin may be one of these, but larger studies are needed to prove its accurate utility in epithelial ovarian cancer. Finding the particularities of serous type of ovarian cancer which secrete inhibin may lead to some conclusions. Also, it is essential to determine the mechanism through which inhibin level is increased in women with epithelial ovarian cancer.

Keywords: *inhibin, epithelial ovarian cancer, serum marker*

Rezumat

Cancerul ovarian este una dintre cele mai frecvente cauze de deces la femei, iar cancerul ovarian epitelial este cel mai frecvent tip. Este diagnosticat adesea într-un stadiu clinic avansat (stadiul III sau IV), iar rata de supraviețuire pe termen lung este scăzută. Unul dintre motive este că testele de diagnostic disponibile au specificitate și sensibilitate limitate. Detectarea precoce a cancerului ovarian este cheia pentru reducerea mortalității și morbidității. Este cunoscut faptul că CA 125 este utilizat pentru diagnosticarea și urmărirea cancerului ovarian epitelial, iar inhibina este un marker sensibil pentru tumorile mucinoase și de granuloasă ale ovarului. Există însă unele studii care sugerează că inhibina este crescută și la unele femei aflate în postmenopauză, cu tumori ovariene epiteliale. Inhibina este un hormon ovarian implicat în reglarea fertilității, fiind nedetectabilă la menopauză. Creșterea sa la femeile aflate în postmenopauză cu cancer ovarian epitelial a condus la o serie de studii care au evaluat posibilitatea ca inhibina să fie un marker seric pentru cancerul ovarian epitelial. În ciuda numeroaselor cercetări, nu a fost încă stabilit un rol exact al inhibinei în cancerul ovarian epitelial. Este acceptat faptul că unele combinații de biomarkeri pot îmbunătăți detectarea cancerului ovarian. Inhibina poate fi unul dintre aceștia, dar sunt necesare studii mai mari pentru a demonstra utilitatea exactă a acesteia în cancerul ovarian epitelial. Descoperirea particularităților tipului de cancer ovarian seros care secretă inhibină poate duce la unele concluzii. De asemenea, este esențial să se determine mecanismul prin care are loc creșterea nivelului de inhibină la femeile cu cancer de ovar epitelial.

Cuvinte-cheie: *inhibină, cancer ovarian epitelial, marker seric*

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Este inhibina un marker serologic util pentru femeile la postmenopauză cu cancer ovarian epitelial?

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Ovarian cancer is the second most common gynecologic cancer in developed countries and the third most common gynecologic malignancy in developing countries[(1)]. Of all ovarian malignancies, 95% are of epithelial type, developed from epithelial cells. It represents the fifth leading cause of death in women in Europe and the United States[(2)]. The disease is usually diagnosed in an advanced stage. This is due to the non-specific symptomatology, which appears when cancer has already spread throughout the abdominal cavity, and the lack of some specific options for screening. Despite significant effort to develop new therapies, late diagnosis is still associated with a low treatment efficacy and a high mortality. Although during the years new diagnostic or screening methods for epithelial ovarian cancer have been introduced on a regular basis, these did not significantly improve the treatment outcome[(3)].

Early diagnosis is still the best option to reduce mortality caused by epithelial ovarian cancer (EOC). More specific strategies for screening and diagnosis

should have a great impact in the treatment outcome. In addition, it is considered that finding some prognostic factors should be useful for selecting the patients with poor prognosis for a more aggressive therapy[4,5].

The combination of CA 125 and vaginal ultrasonography is the most frequently used screening strategy for the patients with family history of ovarian cancer. Moreover, researchers have tried to combine other serum markers (HE4, inhibin, CEA, CA 19-9) or multimodal tests to improve the detection of malignant pathology of the ovary. Not all strategies could show a high sensitivity and specificity for the diagnosis of epithelial ovarian cancer. They are associated with a high rate of false-positive tests and the risk of more invasive testing and treatment[6]. Some studies reveal that combinations of biomarkers and imaging may improve ovarian cancer detection, but further studies are needed to validate these hypotheses[6,7].

There are some reports in the literature on inhibin level in women with epithelial ovarian carcinoma[4,8]. It is known that the serum total inhibin is a sensitive marker for diagnosis and monitoring of mucinous and granulosa-cell tumors of the ovary. Its levels decrease significantly after surgery and increase in case of recurrence. But some studies reflect that inhibin is also elevated in epithelial ovarian tumors[9].

Inhibins are members of the transforming growth factor beta (TGFb) family, a group of growth factors with similar structure but with different functions. Inhibin is synthesized as a dimeric glycoprotein consisting of an *a* subunit and one of two *b* subunits (bA, bB). The complex a/bA is called inhibin A, and the complex a/bB is known as inhibin B[10,11].

Inhibin A is produced by the dominant ovarian follicle and the *corpus luteum*. Inhibin B, on the other hand, is released from the smaller follicles[12]. More exactly, inhibin has been isolated from follicular fluid and is produced by the granulosa cell layers of the follicle[13,14]. It is produced by the ovaries and secreted into the bloodstream and behave as an endocrine factor. It specifically inhibits the secretion of the follicle-stimulating hormone (FSH), a pituitary hormone which promotes ovarian folliculogenesis. In turn, FSH stimulates inhibin production in the gonads, regulating fertility through a FSH-inhibin negative-feedback mechanism[9]. At menopause, with the depletion of ovarian follicles, serum inhibin levels decrease to nondetectable levels and serum FSH increase[9,12].

It is established that inhibin serum level is a useful test for detecting and monitoring the recurrence of granulosa-cell tumors (GCT) and mucinous tumors of the ovary, but elevated inhibin levels were also reported in women with EOC[9,11,16].

Blaakaer et al. suggested an inverse relationship between serum inhibin and FSH, developing a study on postmenopausal women with epithelial ovarian tumors. They showed the correlation between an elevated inhibin level and a decreased FSH level in the group of women with EOC[15].

On the contrary, in a study on 212 postmenopausal women with suspected ovarian cancer, Healy et al. demonstrated that inhibin concentration was negatively correlated with serum FSH level in women with GCT, but not in women with other ovarian tumors. Also, they showed that 82% of women with mucinous carcinomas had high serum inhibin level and only some women with other types of epithelial ovarian tumors (17% of patients with EOC). The concentrations fell after tumor removal[16].

Also, it was revealed that serous tumors secrete inhibin-related peptides, but not dimeric inhibin A[17]. Other data suggested that serum *a* inhibin precursor (pro-aC) levels were more often raised in women with EOC than dimeric inhibin (A and B), and pro-aC associated with CA 125 may be useful as a biomarker for EOC in postmenopausal women[11].

On the other hand, Frias et al. reported inhibin A as a possible independent prognostic factor for survival in postmenopausal women with EOC[5]. Menon et al. study supported the findings about the preferential secretion of precursor forms of the *a* subunit by EOC, rather than dimeric inhibin A. They didn't agree on the pro-aC as biomarker for EOC due to the fact that only 11% of women had elevated levels[18].

Other studies investigating the total inhibin as serum marker for epithelial ovarian tumors showed that the combination between CA 125 and serum inhibin may be useful for noninvasive diagnosis of EOC[8,19].

Another study evaluated the source of elevated inhibin from ovarian epithelial tumors and the role of the gonadotropin-inhibin/activin relationship in the development of EOC. It concluded that stroma of EOC is the main source of the secretion of serum *a* inhibin. Dimeric inhibin A production may be the result of combined secretion of the α subunit by tumor stroma and the βA subunit by epithelium. However, the mechanism of the inhibin and activin in the development of EOC remained unclear[4,20]. Tournier et al. suggested that inhibin genetic mutation (mutation of the INHBA gene) conducted to the genetic determinism of epithelial tumors[21].

Despite the numerous reviews, an exact role of inhibins (precursors, subunits and mature molecules of inhibin) in epithelial ovarian cancer has not been established yet. It has been recognized that various forms of this type of cancer produce members of the inhibin family, but the precise molecules of these products are not yet defined. The researchers admitted the importance of inhibins in epithelial ovarian tumors, but further studies are needed to prove the clinical utility in the diagnosis, management and prognosis, and also as a factor in the pathogenesis of these tumors.

Due to late diagnosis and high mortality of women diagnosed with ovarian cancer, there is an imperative need for new serum markers for epithelial ovarian cancer which can improve the sensitivity and specificity of markers already used for the early diagnosis and management.

The discovery of a serum marker for epithelial ovarian cancer could represent an important step toward the screening of this disease.

Inhibin may be one of these, but additional and larger studies are needed to establish its accurate utility in epithelial ovarian cancer. It is known that only some EOC have high serum inhibin levels. Finding the particularities of serous type of ovarian cancer which secrete inhibin may lead to some conclusions. Also, it is essential to determine the mechanism through which inhibin levels are increased in women with EOC. ■

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References

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65:87-108.
2. Siegel R, Naishadham D, Jemal A. Cancer statistics. CA Cancer J Clin. 2012;62:10–29.
3. Sharma A, Burnell M, Gentry-Maharaj A, Campbell S, Amso NN, et al. Factors affecting visualization of postmenopausal ovaries: descriptive study from the multicenter United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Ultrasound Obstet Gynecol. 2013;42(4):472–7.
4. Walentowicz P, Krintus M, Sadlecki P, Grabiec M, Mankowska-Cyl A, et al. Serum Inhibin A and Inhibin B levels in epithelial ovarian cancer patients. PLoS One. 2014;9(3):e90575.
5. Frias AE Jr, Li H, Keeney GL, Podratz KC, Woodruff TK. Preoperative serum level of inhibin A is an independent prognostic factor for the survival of postmenopausal women with epithelial ovarian carcinoma. Cancer. 1999;85(2):465-471.
6. Ueland FR, Li AJ, Goff B, Chakrabarti A. Serum biomarkers for evaluation of an adnexal mass for epithelial carcinoma of the ovary, fallopian tube, or peritoneum. Available at: https://www.uptodate.com/contents/serum-biomarkers-for-evaluation-of-an-adnexal-mass-for-epithelial-carcinoma-of-the-ovary-fallopian-tube-or-peritoneum
7. Anastasi E, Gigli S, Ballesio L, Angeloni A, Manganaro L. The complementary role of imaging and tumor biomarkers in gynecological cancers: An update of the literature. Asian Pac J Cancer Prev. 2018;19(2):309-17.
8. Tsigkou A, Marrelli D, Reis FM, et al. Total inhibin is a potential serum marker for epithelial ovarian cancer. J Clin Endocrinol Metab. 2007;92(7):2526-31.
9. Robertson DM, Oehler MK. Emerging role of inhibin as a biomarker for ovarian cancer. Womens Health (Lond). 2005;1(1):51-7.
10. de Kretser DM, Robertson DM. The isolation and physiology of inhibin and related proteins. Biol Reprod. 1989;40(1):33-47.
11. Lambert-Messerlian GM, Steinhoff M, Zheng W, et al. Multiple immunoreactive inhibin proteins in serum from postmenopausal women with epithelial ovarian cancer. Gynecol Oncol. 1997;65(3):512-6.
12. Kumanov P, Nandipati KC, Tomova A, Robeva R, Agarwal A. Significance of inhibin in reproductive pathophysiology and current clinical applications. Reprod Biomed Online. 2005;10(6):786-812.
13. Ling N, DePaolo LV, Bicsak TA, Shimasaki S. Novel ovarian regulatory peptides: inhibin, activin and follistatin. Clin Obstet Gynecol. 1990;33(3):690-702.
14. Robertson DM. Transforming growth factor beta inhibin family. Baillieres Clin Endocrinol Metab. 1991;5:615-634.
15. Blaakaer J, Micic S, Morris ID, et al. Immunoreactive inhibin-production in post-menopausal women with malignant epithelial ovarian tumors. Eur J Obstet Gynecol Reprod Biol. 1993;52(2):105-10.
16. Healy DL, Burger HG, Mamers P, et al. Elevated serum inhibin concentrations in postmenopausal women with ovarian tumors. N Engl J Med. 1993;329(21):1539-42.
17. Burger HG, Robertson DM, Cahir N, et al. Characterization of inhibin immunoreactivity in post-menopausal women with ovarian tumours. Clin Endocrinol (Oxf). 1996;44(4):413-8.
18. Menon U, Riley SC, Thomas J, et al. Serum inhibin, activin and follistatin in postmenopausal women with epithelial ovarian carcinoma. BJOG. 2000;107(9):1069-74.
19. Dubbewar A, Pathak B, Biswas M, Malhotra G. Combined use of CA 125 and Inhibin as tumor marker for detection of ovarian cancer in comparison to CA 125 or Inhibin alone. Int J Reprod Contraception Obstet Gynecol. 2017;6(12):5313-6.
20. Zheng W, Lu JJ, Luo F, et al. Tumor stroma as the main source of inhibin production in ovarian epithelial tumors. Am J Reprod Immunol. 2000;44(2):104-13.
21. Tournier I, Marlin R, Walton K, Charbonnier F, Coutant S, et al. Germline mutations of Inhibins in early-onset ovarian epithelial tumors. Hum Mutat. 2014;35(3):294-7.