INVITED COMMENTARY

Is inhibin a serum marker for ovarian cancer?

Geralyn M Lambert-Messerlian

Department of Pathology and Laboratory Medicine, Division of Prenatal and Special Testing, Women & Infants Hospital, Brown University School of Medicine, 101 Dudley Street, Providence, RI 02905, USA

(Correspondence should be addressed to G M Lambert-Messerlian, Email: gmesserl@wihri.org)

Research endocrinologists are well aware of inhibin and the family of proteins of which it is a part. Inhibin was discovered almost 70 years ago as a product of the gonads that selectively inhibited the secretion of follicle-stimulating hormone (FSH) at the level of the pituitary gland. We now know that inhibin is present in at least two biologically active forms (inhibin A and B) as well as in a variety of α subunit precursor forms and has been implicated not only in endocrine functions, but also as a possible local growth regulator in a variety of tissues. In clinical endocrinology, inhibin B appears to be a useful tool in assessing ovarian reserve and the potential for success in assisted reproduction. Research endocrinologists may not be aware, however, of the developing use of circulating inhibin levels as a diagnostic aid in clinical areas outside endocrinology. For example, in the area of prenatal genetic diagnosis, the measurement of inhibin A has been shown to be useful in maternal serum screening for Down's syndrome pregnancy in the second trimester. In the area of gynecologic oncology, exemplified by the study of Ala-Fossi and colleagues (1) in this issue of the *European Journal of Endocrinology*, various forms of inhibin are being tested and applied as possible serum markers of ovarian cancer.

Inhibin looked promising as a new ovarian cancer marker in the early 1990s when Healy *et al.* (2) showed that serum levels were elevated in 29% of 143 postmenopausal women with confirmed ovarian cancer. The inhibin antibody (Monash No. 1989) used for the radioimmunoassay in that study was directed exclusively to the α subunit (3) and detected a combination of biochemical forms otherwise known as total inhibin, that included dimeric inhibin A and B as well as α subunits (4). With the advent of more specific inhibin assays, recent studies have been aimed at determining which form (total inhibin, inhibin A, inhibin B, or the α inhibin subunit precursor as measured by the pro- α C assay) might be the best marker of disease.

The most coherent and convincing data that serum inhibin levels are useful as a marker of ovarian cancer come from studies of granulosa cell tumors. All forms of inhibin are elevated in the serum of patients with granulosa cell tumors relative to healthy women of the same age (2, 5). This finding has a sound pathophysiological basis since the granulosa cell is the primary origin of inhibin synthesis. There have

been subtle differences in the frequency of elevated levels depending on the biochemical form(s) measured: 100% for total inhibin, 89–100% for inhibin B, 90% for pro- α C, and 71–77% for inhibin A (2, 5, 6). Nevertheless it is clear that both α subunit and dimeric forms of inhibin are secreted in abundance in granulosa cell tumors, with total inhibin, a combination of all forms, most reliably increased.

There is a consensus that α inhibin is a better serum marker than dimeric inhibin for all cases of epithelial ovarian tumors, and this is further supported by the study of Ala-Fossi *et al.* (1) in the present issue of this Journal. Inhibin appears to be a suitable serum marker for epithelial tumors of the mucinous type with about 70–80% of patients having elevated total inhibin (2, 5, 7), 55–60% having elevated inhibin B or pro- α C, and 20% having elevated inhibin A levels (5). In contrast, inhibin is not a very good marker in non-mucinous epithelial tumors. While mucinous tumors characteristically include benign ovarian type stroma which is believed to be a source of inhibin (8), most serous, clear cell and endometrioid carcinomas typically lack such ovarian stroma. At best, total inhibin is elevated in 15–35% and pro- α C is elevated in <15%–30% of non-mucinous epithelial ovarian cancer cases (2, 5, 9).

The specificity of the inhibin markers for ovarian cancer has yet to be addressed sufficiently in the literature. Few previous studies have examined cases of non-ovarian cancers or benign disease and the published results suggest rather poor specificity of the inhibin markers. The total inhibin elevation has ranged from 7 to 41% in non-ovarian cancers (2, 5) and 28% in benign gynecologic disease (2, 7). In agreement, Ala-fossi *et al.* (1) found no difference in pro- α C levels in malignant versus benign ovarian disease.

Therefore, inhibin's utility appears to be limited to monitoring of patients with known ovarian cancer. For granulosa cell tumors, inhibin has been shown to decrease after surgery and to increase with disease recurrence (2, 10). In fact, some patients have a documented rise in inhibin 11 months preceding recurrence of granulosa cell ovarian cancer (11). Neither inhibin A nor inhibin B levels were elevated in granulosa cell tumor patients in remission (6). However, it remains to be investigated whether α

inhibin levels will serve as a marker of tumor recurrence for epithelial ovarian cancer. Although inhibin levels declined shortly after surgery in patients with mucinous tumors (2, 7), no long-term studies have followed inhibin levels in women with epithelial ovarian cancer. Other data are discouraging; for example, patients with epithelial ovarian cancer had similar levels of inhibin A and inhibin B regardless of whether they had progressive disease or were in remission (6).

The question of inhibin's utility as a prognostic indicator for ovarian cancer is in its infancy. One previous study suggested that inhibin A levels were prognostic of disease, with higher levels associated with poor survival (12). The data were not convincing however, with a median inhibin A level (1.21 pg/ml) below the reported assay sensitivity. Furthermore, it is doubtful that inhibin A, the least effective marker of all the inhibin biochemical forms, would be prognostic of disease. Ali-Fossi *et al.* (1) examined the question of prognosis and found no relationship between serum inhibin levels and prognosis. In contrast, results in peritoneal fluid suggested that high inhibin A or pro- α C levels were associated with a better prognosis, defined as lower stage and tumor grade. This finding was likely confounded by the small number and mixed histologic subtypes of the cases studied. For example, inhibin levels are frequently elevated in mucinous tumors, which are typically better differentiated and have a better prognosis than other epithelial tumors, while serous type tumors are typically negative for inhibin and highly aggressive. It is therefore probable in a small study that the prognosis is more a function of the tumor histology than the inhibin level.

There are some practical concerns with the use of total inhibin as an ovarian cancer marker. The majority of the data collected have been obtained using the Monash total inhibin polyclonal antiserum which has essentially been depleted. There are alternative α inhibin assays available, such as the pro- α C (Serotec, UK), Medgenix Diagnostics (Fleurus, Belgium), or α C immunofluorimetric assay (13), but none of these has been extensively tested as an ovarian cancer marker. Regardless of the assay chosen, it is essential that both a premenopausal and postmenopausal normal range be established since inhibin levels vary greatly with reproductive status, and it is noteworthy that much of the data collected on inhibin as a tumor marker has been limited to postmenopausal women. This limitation applies to peritoneal fluid as well as to serum. Peritoneal fluid inhibin levels are reported to change in relation to the menstrual cycle and were previously reported at much higher concentrations (14) than reported by Ala-Fossi *et al.* (1) in their postmenopausal group of women.

Ironically, the investigation of inhibin as an ovarian cancer marker using more specific immunoassays has brought us back to where we started with the less

specific, total inhibin immunoassay. Total inhibin seems to be the best serum marker studied to date, detecting all cases of granulosa cell tumors, 70–87% of the mucinous tumors and about 15–35% of other epithelial tumor types. Inhibin is complementary to CA 125 as an ovarian cancer marker (9, 13) since it performs best for the two types of ovarian cancer that CA 125 detects least well, mucinous and granulosa cell. Monitoring postmenopausal women with granulosa cell tumors is clearly the most promising use of inhibin, but further studies are needed to document the specificity of inhibin and its response in recurrent epithelial ovarian cancer, and to determine the most appropriate α inhibin assays for this purpose.

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