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Gonadotrophin Levels in Postmenopausal Women with Epithelial Ovarian Cancer

Chinmoy Kumar Bose, Usha Menor, Janice M Thomas, Anne B Dawnay, Ian J Jacobs

St. Bartholomew's Hospital, The Royal London Hospital Trust, West Smithfield, London EC1A 7BE

Summary

Follicle Stimulating Hormone (FSH) and luteinising hormone (LH) levels were assayed in stored serum samples collected pre-operatively from 19 postmenopausal women with epithelial ovarian cancer. Each case was matched for age with 2 controls with no history of hormone replacement therapy, from a population of healthy, postmenopausal women who had enrolled in a screening study. FSH levels were significantly lower in women with ovarian cancer than in controls ($p<0.02$) but there was no difference in LH levels. The results are consistent with a role for gonadotrophins in the aetiology of ovarian cancer.

Introduction

A number of in vivo and in vitro studies have supported the suggestion by Biskind and Biskind (1944) that elevated gonadotrophin concentrations may contribute to the development of malignant ovarian tumours. The highest incidence of ovarian cancer occurs in the postmenopausal period when gonadotrophins attain high blood levels due to the lack of feedback from ovarian steroid hormones. In 1979 Ylikorkala et al could not find any change in serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels in the serum of patients with malignant epithelial ovarian tumour and opined that there is no relation between pituitary function and ovarian tumour. Mahlek et al (1990) observed lowering of both FSH and LH levels in such patients while Blaakaerr et al (1992) found consistent lowering of FSH and LH remaining unchanged. However gonadotrophin releasing hormone (GnRH) agonist, triptorelin, has failed to produce any relevant beneficial effect in patients with advanced ovarian cancer who received standard surgical cytoreduction and cytotoxic chemotherapy in a fairly large prospective double blind randomized trial. Emons et al (1996). While evidence is conflicting, a critical role for gonadotrophins in the genesis and progression of ovarian cancer cannot be ruled out. Our present study aims to assess serum gonadotrophins (FSH & LH) levels in postmenopausal women with epithelial ovarian cancer (EOC).

Methods

A retrospective controlled trial was planned to compare preoperative serum FSH and LH levels in women with EOC and age matched postmenopausal women. In this study, we used stored serum samples from our serum bank situated in the Gynaecological

Cancer Research Unit of St Bartholomew's Hospital. So, we did not find it necessary to take approval of our ethical committee. Twenty four cases of ovarian cancer were diagnosed since the middle of 1994 from the list of patients with gynaecological ailments who donated blood to the serum bank of our unit before they were operated in the Department of Gynaecological Oncology of our hospital. For every cancer case two controls (n=48) were selected from the women who enrolled in the population screening programme of our unit and donated blood to our serum bank. Amongst 24 sets five sets of case and controls were excluded from the study because of no serum or insufficient serum was available or because the patient was found to be premenopausal. Thus, 19 cases with 38 controls were available for the study. All women of both the groups were postmenopausal with no history of hormone replacement therapy and no other malignancies. Except ovarian cancer in the study group all women were otherwise healthy and they were free from hepatic or renal disorders. The study group (48-86 years, X=64.8 years) were age matched with the control group (52-80 years, X=65 years). Ovarian cancer cases were histologically proven epithelial ovarian cancer (4 mucinous, 9 serous, 2 borderline, 2 endometrioid and 2 adenocarcinoma unspecified). Staging was done on laparotomy according to the International Federation of Gynaecology and Obstetrics (FIGO). They were as follows: stage I-3 cases, stage II-3 cases, stage III-9 cases and stage IV-2 cases.

Laboratory assay

Serums were deep frozen at -20 C until they were thawed for the study. Gonadotrophic activity in serum is usually unaffected by keeping the serum sample deep frozen for years or by repeated thawing and freezing of the serum (Wide, 1976). Serum FSH and LH were measured by using heterogenous sandwich magnetic assay (MSA) method using commercial kit of Technicon Immuno[®] system (Bayer Corporation, New York, USA). Unit were expressed in IU/L. Quality control was done by using Technicon Test point[TM] ligand controls at the beginning of the shift and all tests were done in the same day at a time.

Results

Table I shows the mean of serum levels of FSH and LH with their confidence interval. A significant difference was observed in case of the serum FSH level between healthy control and women with epithelial ovarian cancer. But in case of LH this difference was not statistically significant. Two sample t test with pooled standard deviation was used as there was considerable similarity in standard deviations of both FSH and LH in different groups and the data seemed to be normally distributed. It was being shown by a F test also where ratio of squared standard division did not produce any significant difference. However, non parametric Mann Whitney U test was also done to compare the result. Serum FSH levels were found to be significantly lower ($p<0.02$) in epithelial ovarian cancer patients while the LH values were similar in both the study and the control group. The median with their non-parametric confidence intervals at 95% level were also assessed for each group and they were as follows. In the control group FSH had a median of 87.5 IU/L with a confidence interval 79.6-97.9 IU/L and LH had a median of 38.8 IU/L, confidence interval being 28.5-42.7 IU/L. Likewise, in study group, FSH was found to have a median of 49.7 IU/L with confidence interval 32.3-72.8 IU/L and LH had a median of 40 IU/L and confidence interval 21.3-51 IU/L.

Discussion

In our study we have detected significantly lower FSH levels in postmenopausal epithelial ovarian cancer than those found in healthy post menopausal patients. No such difference was noticed in case of LH levels. Our finding corroborates earlier finding of Blaakaer et al (1992). They found considerably higher significance of this difference in FSH level while half of their series of 28 cases of postmenopausal epithelial ovarian cancer was of stage I. But instead of radioimmunoassay, heterogenous sandwich magnetic assay was used to determine FSH and LH levels in our study. Hence, it seems that earlier a stage lower is the level of FSH. There is no consistent report of either HCG stimulation or oestradiol/androstenedione negative

Table I: Serum level of FSH and LH in control and study group expressed as mean with 95% confidence interval (parametric test).

	FSH (IU/L)	LH (IU/L)
Control	80.6	36.4
N=38	(69.3-91.6)	(31.5-41.3)
EOC	54.4*	32.6
n=19	(38.0-70.8)	(23.3-41.9)

*p< 0.02, degree of freedom 55.

feedback to explain significant lowering of FSH with LH remaining unchanged. Central depression of gonadotrophin release by dopaminergic system as a cause is ruled out due to the fact that the levels of thyrotrophin stimulating hormone (TSH) or prolactin remain unaffected as shown by previous study (Blaakaer 1992). Biologically active dimeric inhibin A may reduce FSH level. But, in serous epithelial ovarian carcinoma, which is the most common ovarian tumour, inhibin A was not found to be high. (Wallace & Healey 1996). However, there is no report of inhibin B level in such women and such a study is necessary. After the failure of gonadotrophin releasing hormone agonist to have any beneficial effect in such cancers the role of pituitary has become more subtle. It is true that the pituitary may secrete FSH of different biological activity and tumour production of hormone or hormone fraction may exert modulating or even inhibitory effect on gonadotrophin or on its biological activity. But failure to secrete more FSH might not be the inadequacy, rather, this might be a protective phenomenon or a defensive mechanism also. In other words, this consistent lowering of FSH may be an effort on the part of the pituitary to check incessant growth of ovarian cancer in a milieu of high follicle stimulating hormone receptor (FSHR) expression in the malignant epithelial tumour tissue. Indeed, strong expression of FSHR is currently noticed in both the normal surface epithelium and the malignant epithelium of human ovary (Zeng et al, 1996 and Ichikanth et al, 1996). It is known that pituitary may autoregulate the secretion of FSH and may even secrete it without any stimulation. Thus regulation of FSH secretion and FSHR expression may still be important in such cancers and the study is currently under way.

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