GNRH-TEST IN MENOPAUSE

Its possible use in identifying the subjects at risk for dysplastic endometrial pathology

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SUMMARY

The Authors, after reviewing the results of their previous studies on the endocrine situation in post-menopausal endometrial carcinoma and considering what emerges from the present work, suggest GnRH-Test as a mean to better identify the subjects at risk for this neoplasia; in patients already affected with endometrial cancer, it could be an indirect index in recommending or not endocrine therapy.

The several epidemiological studies carried out on endometrial cancer-affected patients clearly pointed out that this neoplasia is mostly a problem of peri- and post-menopausal ages.

Its prevalent incidence in a period of female life when ovarian function progressively exhausts with a consequent fall in ovarian estrogens, is justified by the persistent estrogen-stimulation of endometrial receptors, which is quantitatively reduced but now free from the modulation by Progesterone, the most powerful natural anti-estrogen.

The chronic unopposed estrogen-stimulation on a prepared back-ground can probably induce endometrial dysplastic or neoplastic degeneration ([1, 2, 3, 4]).

If, however, every woman experiences menopause, not everyone will be affected with endometrial cancer; the problem, then, is to detect the risk-factors for this neoplasia: some seem already identified: diabetes, hypertension, and mainly obesity ([5]).

The fact is generally acknowledged that peripheral conversion of Androstenedione to Estrone is markedly higher in overweight than in normal-weight subjects, and that estrogen plasma-levels are not always higher in endometrial cancer-affected patients compared to controls ([4, 9, 10, 11, 12]) while they are correlated with the percentage of the ideal weight ([13, 14]), independently on the presence of this neoplasia.

These considerations make us consider little useful a simple assay of basal estrogen plasma-levels to correctly identify subjects at risk for endometrial malignancy, while this aim could be better achieved through the use of dynamic tests, such as GnRH-Test recently proposed by Geller ([15]) in the prophylaxis of breast carcinoma.

MATERIAL AND METHODS

We studied fourty post-menopausal patients admitted to the Obstetric and Gynecological Clinic of Padua University: they were divided

Clin. Exp. Obst. Gyn. - ISSN: 0390-6663
VIII, n. 3, 1981

into two groups: 20 control patients, free from any endometrial pathology after a careful histologic examination (mean age = 57.05±1.75 (SEM) years; post-menopausal for 86.65±17.78 (SEM) months); 20 patients affected with histologically proved endometrial cancer at different clinical stages (mean age = 60.42±1.94 (SEM) years; post-menopausal for 131.12±18.43 (SEM) months); each patient underwent, between 08.00 and 10.00 of three consecutive days, blood sample drawings for basal assays of E2, FSH, LH plasma-levels.

After the third day basal drawing, a stimulation was done with GnRH 100 mcg (Relisorm) in one rapid intravenous administration; blood samples were drawn at 15, 30, 60 minutes from the injection, to assay the same-hormone levels.

The heparinized samples were centrifuged for five minutes and then stored at a temperature of −20 °C until the assay. RIA was carried out of 17-β-E2, FSH and LH, by methods already described elsewhere ([12]).

RESULTS

The hormone basal levels in the affected and control patients appear in the upper part of fig.s 1 and 2, in which the response-area integrals for both gonadotropins are graphically represented; in control patients the FSH response-area integral (5720.62) is greater than the LH response-area integral (4267.42); in endometrial cancer-affected patients the FSH response-area integral (4425.75) is smaller than the LH response-area integral (7734.97).

E2 plasma levels in control patients are well correlated with the percentage of the ideal weight ($r=0.587$; $p<0.01$); the same is true in the affected patients ($r=0.608$; $p<0.01$).

The range of the patients' weight, expressed through the percentage of the ideal weight, was 94-155% in the controls and 105-212% in the affected patients.

DISCUSSION

E2 levels we found high in endometrial cancer-affected patients, in agreement with several Authors ([4, 9, 10, 11, 12]), are correctly justified by the higher number of overweight subjects in the cancer group (weight range = 105-212% of the ideal weight) than in the control group (weight range = 94-155% of the ideal weight) ([14]); they don't seem actually correlated to the presence of endometrial pathology. Higher LH than FSH basal plasma levels in both groups seem consistent with E2 levels, even if Geller ([15]) had different results: he found higher FSH than LH basal plasma levels also in subjects who had been post-menopausal for less than two years, in which a good estrogen impregnation can still be hypothesized.

In our study, the higher LH than FSH response to GnRH (area integral) we found in cancer patients, could be correlated to E2 higher plasma levels, in agreement with Yen's theory ([16]) according to which circulating estrogens increase hypophyseal GnRH-Receptors.

The importance of estrogen plasma levels in the kind of response to GnRH has already been, however, clinically documented by several Authors ([17, 18, 19]) who showed, for instance, different responses to the test depending on when it was performed: in the early follicular phase (low estrogen and E2-Receptor levels) or in the periovulatory phase (high estrogen and E2-Receptor levels).

Indeed, not only the current estrogen plasma levels seem to condition the hypophyseal response to GnRH: in 1974 Evans and Coll. ([20]) evidenced the presence of E2-Receptors in the atrophic endometria of subjects who had been post-menopausal for many years, and more recently Greenblatt ([21]) reported the presence of estrogen-Receptors in the hypothalamus, hypophysis and uterus, which persist for long time after estrogen disappearance.

Otherwise, Geller's ([15]) researches, which point out that post-climateric preferential LH-release can be found in subjects who underwent surgery because of uterine fibroids or polycystic ovaries (hyperestrogen-dependent situations), seem to further support the hypothesis that also E2 past

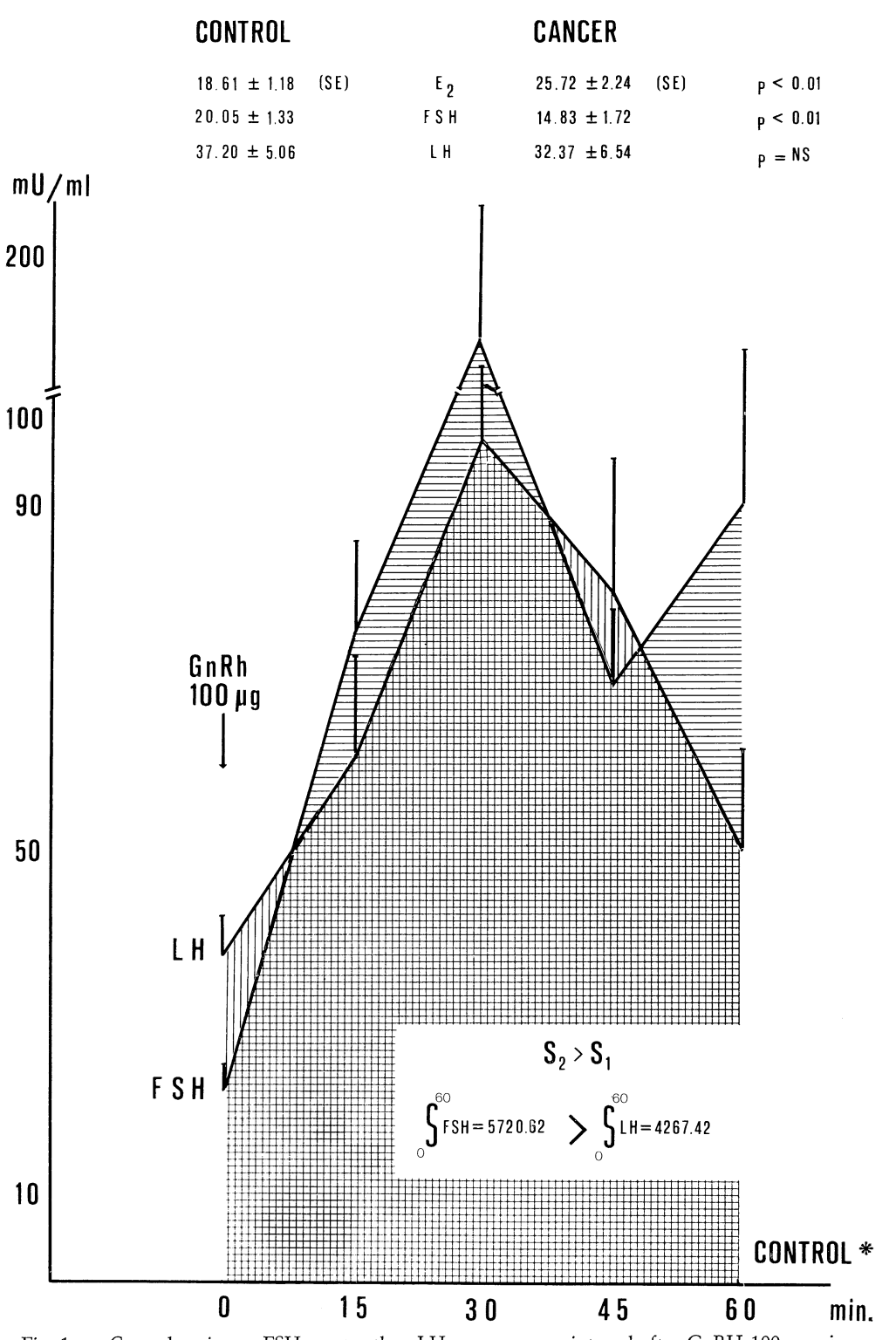

Fig. 1. — Control patients: FSH greater than LH response-area integral after GnRH 100 mcg i.v.

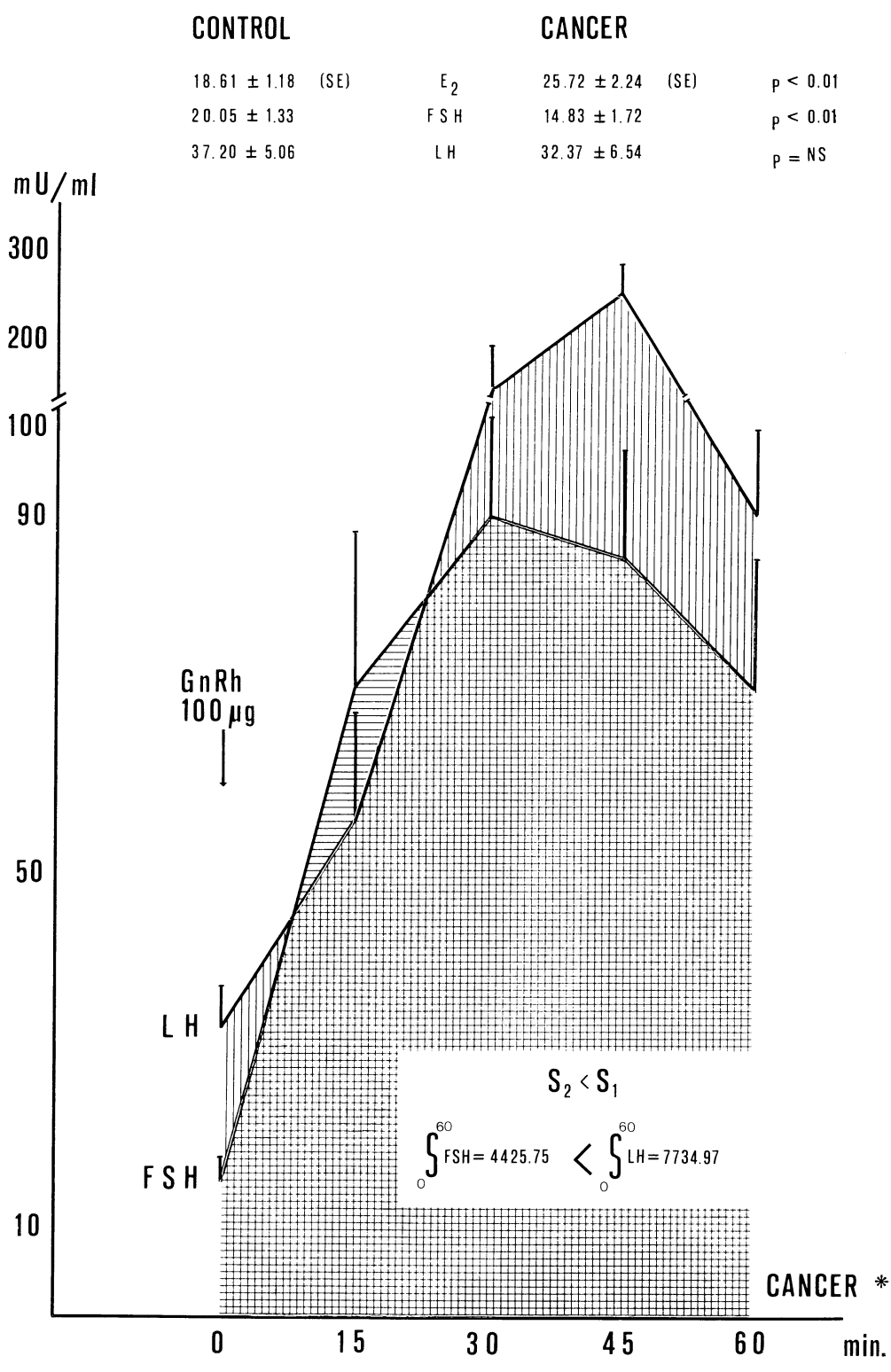

Fig. 2. — Cancer patients: LH greater than FSH response-area integral after GnRH 100 mcg i.v.

impregnation, as well as its actual circulating levels, can condition the hypophyseal response to GnRH.

The possibility ([22]) that LH preferential release is linked to a focal hypophyseal hyperplasia sometimes associated with microalterations of the sella, was not verified in our study as our patients did not undergo a polytomography of the sella turcica.

CONCLUSIONS

At the end of this work the following considerations seem to summarize our current opinion:

1) indepedently on FSH and LH basal levels, LH preferential release in post-menopausal patients affected with endometrial cancer is related to their higher E2-plasma levels;

2) LH preferential release in endometrial cancer-affected patients is not dependent on the malignancy itself, but on situations which determine an increase in E2-production, such as overweight which is greater in them than in the controls;

3) in subjects at risk for endometrial carcinoma (precocious menarche, delayed menopause, obesity), independently on basal E2-plasma levels, GnRH-Test is useful, as an eventual LH greater than FSH response-area integral will prove the increased risk connected with a higher-degree estrogen-impregnation;

4) LH preferential release following GnRH-Test in patients affected with endometrial cancer could be considered an indirect index of its hormone-dependence, and consequently suggest hormone-therapy for it.

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