Combined effects of clomiphene and GnRH on the regulation of gonadotropins incretion

by

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Clomiphene is known to stimulate gonadotropins incretion by the pituitary (see [1] for a review of the literature). The drug does also induce LH peaks in some cases of anovulation [2, 3, 4, 5] and has been proposed as an investigation tool in hypogonadic conditions [6].

In several cases, the increase in serum levels of LH induced by clomiphene is not effective in the triggering of the ovulation process [7]. The explaination may lay with an inappropriate timing of LH release, related to follicle maturation, as postulated by Yen and Coll. [4] in cases of polycystic ovary. In some other cases, however, an inadequate LH response might be the cause of the failure. Since LH incretion stimulated by clomiphene is believed to follow a LH RH discharge from the hypothalamus, which, in turn, stimulates the pituitary [8], either an hypothalamic or a pituitary disorder, or both might be responsible for the inadequate LH incretion.

With these perspectives, we have studied a group of amenorrheic women in fertile age, assessing their response to the administration of a synthetic gonadotropins releasing hormone (GnRH) and investigating whether and in which measure it was then possible to enhance gonadotropins serum levels by clomiphene and by a subsequent administration of a second dose of GnRH. In fact it is known that clomiphene potentiates GnRH effect on gonadotropins [9] and that the combined effect of the drug and of the synthetic hormone elicits ovulation in some cases of feminine sterility [10].

MATERIALS AND METHODS

Eight women aged between 17 and 30, amenorrheic from several months or years were selected for the investigation. Obstetric and gynecological investigation did not disclose any organic reason for the amenorrhea.

Gonadotropins were determined in serum by the methods described by Midgley [11, 12]. The reagents for the radioimmunological determinations were obtained from Serono Immunochemicals, Rome. The stimulation test with GnRH was performed according to the schedule previously described [13]. The patients considered in the present investigation received each time 100 mcg of a GnRH obtained by Hoechst Italia, Milan. The investigation program was the following. Pituitary response to GnRH was previously studied. 20 to 30 days later the

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patients received clomiphene (Clomid, Richardson Merrell) at the daily dose of 100 mg for five days. On the fourth day after clomiphene discontinuation a second GnRH test was performed.

RESULTS

After clomiphene administration LH serum levels were considerable higher than before the treatment, in all except one case. Also FSH levels were enhanced,

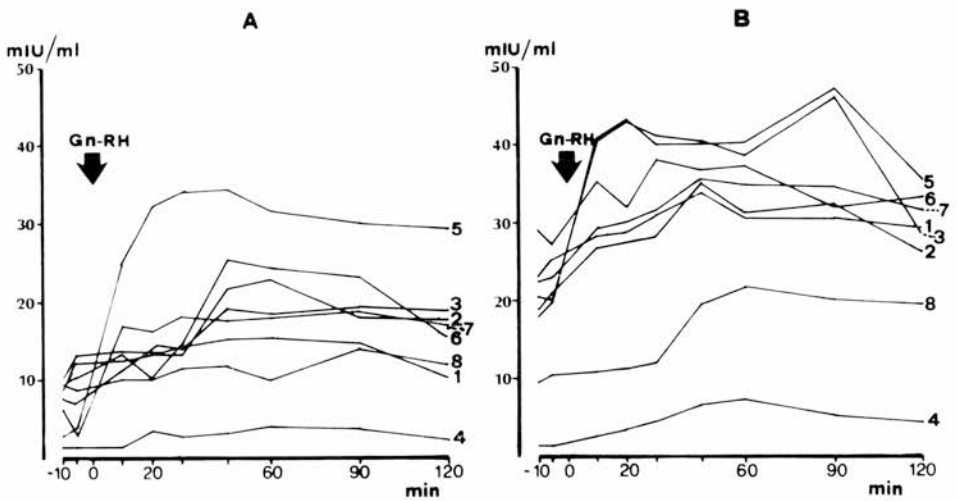

FIG. 1 - Behaviour of LH after stimulation with 100 mcg of GnRH: in A: before clomiphene treatment; in B: after discontinuation of clomiphene.

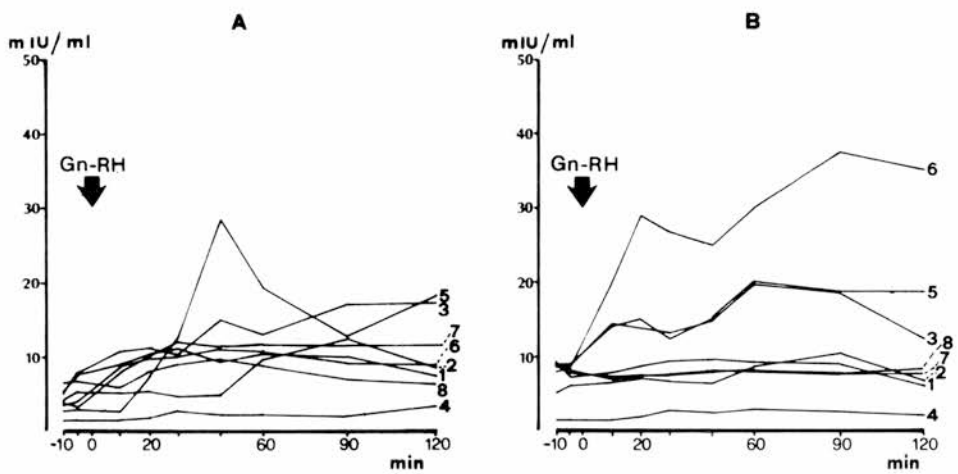

FIG. 2 - Behaviour of FSH after stimulation with 100 mcg of GnRH: in A: before clomiphene treatment; in B after discontinuation of clomiphene.

though the increase was less evident. The case that showed unchanged LH levels did not exhibit any increase in FSH.

The response to GnRH administration showed in six out of eight cases a significant increase in LH. Two cases did not exhibit significant response. Changes in FSH were less conspicuous, except in one case. GnRH administration after clomiphene treatment induced a further significant increase in LH serum levels in seven cases. It should be stressed that one of the unresponsive cases in the first GnRH test did respond with a twofold increase in LH to GnRH administered after clomiphene. FSH changes in the response to GnRH after clomiphene

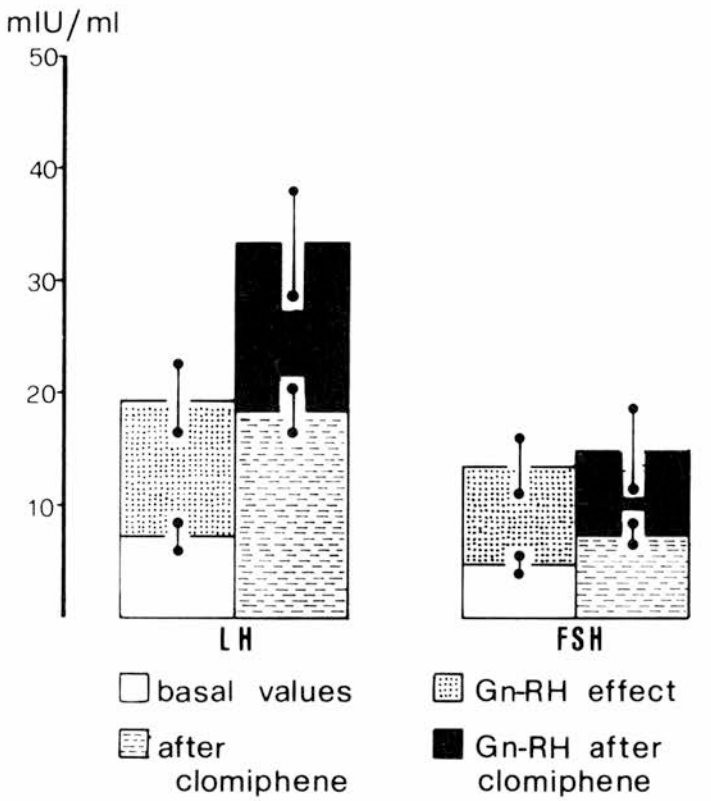

FIG. 3 - Mean values of LH and FSH (and standard deviation) before any treatment, after GnRH administration, after clomiphene and after GnRH administration subsequently to clomiphene discontinuation.

concerned three cases that showed a significant peak and one case that responded to GnRH with a FSH peak before clomiphene administration and did not respond after the anti-estrogen treatment. The data are reported in the figures 1 to 3.

DISCUSSION

The results obtained by the administration of a synthetic gonadotropins releasing hormone confirm that amenorrheic women do not respond homogeneously to this hormone, as it has been already shown. It has been argued that poorly

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responsive cases have a pituitary deficiency, while the possibility to obtain a pituitary response in cases with low basal levels of gonadotropins indicates a primar hypothalamic disorder ([13, 14]). In the latter case, however, the doubt may persist as to the possible effect of a larger dose of releasing hormone.

Of the studied cases, only one did not show any change in gonadotropins serum levels in any experimental conditions. The other poorly responsive cases exhibited a gonadotropin response in at least one of the above mentioned conditions. These findings are mainly related to LH. FSH changes are not easily explainable.

The data obtained indicate that hypothalamo-pituitary axis may be sensitive to stimuli of different kinds and that gonadotropins regulating system consists of several components, that may be differently implicated by pathologic processes. Infact, besides the stimulation by exhogenous releasing hormone, gonadotropins ma be increted by the pituitary under the effect of estradiol's physiological increase in the late normal follicular phase of female's cycle. The existence of such an estradiol dependent positive feed-back has been confirmed by the effect of estradiol administration in the same period of ovarian activity ([15, 16]). However, the steroid is also a component of a negative feed-back, in that it inhibits gonadotropins incretion in earlier phases of the follicular period ([17]). An estradiol dependent negative feed-back has also been observed by us ([18]), when the hormone was administered to healthy men. This inhibitory effect of estradiol is believed to act via the suppression of pulsatile LH discharge, which is mediated by LH-RH, stimulated in turn by alpha adrenergic agents and/or dopamine ([17, 19]).

Clomiphene is known to be an antiestrogen agent, competing with estrogens for hypothalamic and pituitary receptors ([20, 21, 22]). Vandenberg and Yen ([8]) suggest that LH rise induced by clomiphene depends on a greater pulsatile LH incretion, obtained by overcoming estrogens inhibition on LH-RH production by the hypothalamus. Also FSH is similarly affected, as it has been remembered by Chatterjee and Coll. ([23]), who revised the data of the literature. These mechanisms may be called upon in looking for an interpretation of the increase of both gonadotropins that we have observed.

The behaviour of serum levels of LH and FSH after clomiphene has been clearly described by Jacobson and Coll. ([24]): a « clomiphene peak » occurs during drug administration and after its discontinuation. Serum levels of gonadotropins, higher than basal values, persist for several days, a « clomiphene nadir » occurring only about six days. The described peak is followed some days later by a second one, with sharply high values of LH, called the « preovulatory peak ». When we administered GnRH during the « clomiphene peak », a further increase of serum gonadotropins was observed in the majority of cases. Our data agree with the ones of Kastin and Coll. ([9]) in normal men and might be the result of a potentiation of GnRH effect, as Kastin and Coll. ([9]) postulated in commenting on their studies with purified porcine LH-RH.

The data available suggest the comparison betweent this effect of clomiphene on GnRH action and the similarly potentiating effect of estrogens on the releasing hormone action observed by Yen and Coll. ([4]). It is perhaps not hazardous to state at this point that in the presence of per se inhibitory levels of estrogens, clomiphene suppression of estrogens' effect on the hypothalamus and on the pituitary mimicks the facilitatory condition dependent by estrogens levels higher enough to induce a positive feed-back effect.

In this line of thought, a clinical condition where anovulation and amenorrhea may depend on estrogen levels insufficient to trigger LH release might take advantage from clomiphene action. Our data confirm the greater effectiveness of the sequential administration of clomiphene and synthetic gonadotropins releasing hormone ([10]).

SUMMARY

In eight cases of amenorrhea clomiphene was administered at the dose of 100 mg for five days. An increase in LH and FSH serum levels was observed in most cases. FSH rise was less conspicuous. In all cases, except one, the administration of a synthetic releasing hormone of the gonadotropins induced a further increase of LH. In some cases also FSH rose. The finding suggest a potentiating effect of clomiphene on GnRH action.

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