Two distinct two-step ranks of progesterone stimulation after three different levels of oestrogen priming. Effect on induction of luteinizing hormone surges in young and climacteric women

A.Cano and J.J.Tarín

Department of Paediatrics, Obstetrics and Gynecology, Facultad de Medicina, Av. Blasco Ibáñez 17, 46010 Valencia, Spain

1To whom correspondence should be addressed

Age and menopausal status were evaluated as potential modulators of the progesterone action in the initiation of the mid-cycle luteinizing hormone (LH) surge in women. Three distinct levels of oestriadiol priming were used, in combination with two different two-step ranks of progesterone stimulation (10/25 mg and 25/50 mg i.m. injections of progesterone in oil, over 2 consecutive days) in two groups of women, ten premenopausals, aged between 18 and 25 years, and 14 postmenopausals, aged between 48 and 57 years. The low, moderate and high levels of oestriadiol priming were defined in the premenopausal group by days 5 and 9 of the cycle, and 0.4 mg transdermal oestriadiol applied in the early follicular phase respectively. The corresponding situation in the postmenopausal women was defined by the absence of treatment, 0.1 mg transdermal oestriadiol, and 0.4 mg transdermal oestriadiol respectively. The oestriadiol patches were maintained for 5 days, and the first progesterone dose administered on day 3 of treatment. Unambiguous LH surges, detected in serum and urine, were restricted to the protocols using 0.4 mg oestriadiol in both groups, with an onset soon after progesterone administration. The surge was higher in the postmenopausal group in serum and urine. The percentage LH increase above baseline, however, was higher in the premenopausal women. The dose of progesterone did not result in any changes in pituitary LH release. Therefore, the oestriadiol threshold for the progesterone stimulatory effect on LH release was similar in both groups. The postmenopausal women did not yield defective LH surges when adequately primed with oestriadiol and progesterone.

Key words: age/LH surges/menopause/oestrogen/progesterone

Introduction

Experimental evidence confirms that exogenous oestriadiol administration in women may induce an increase in both basal and gonadotrophin-releasing hormone (GnRH)-stimulated luteinizing hormone (LH) release that is both dose- and time-dependent (Hotchkiss and Knobil, 1996). Other evidence indicates that progesterone is an important modulator of LH release. However, the details of that modulation are still debated, since the final direction of the effect, either stimulatory or inhibitory, depends on variables which still are partially unclear.

The endocrine scenario in which progesterone exerts its action is one of the variables influencing the effect of the steroid on LH release. For example, the administration of a small amount of progesterone under conditions of an appropriate level of circulating oestriadiol potentiates the oestriadiol-induced LH release in both humans and animals (Hotchkiss and Knobil, 1996). That stimulation is both augmentative and temporal. However, when progesterone is administered to monkeys and women in the presence of lower levels of circulating oestriadiol, only short-lived or null increments of LH secretion are accomplished (Permez et al., 1987; Terasawa et al., 1987). It has been established that the minimum serum oestriadiol concentration necessary to induce a significant increase in LH is a sustained level of 200 pg/ml for at least 50 h (Young and Jaffe, 1976). Few studies, however, have investigated the oestriadiol threshold that delineates such distinct responses to progesterone.

Other variables that modulate the final progesterone effect are the timing of progesterone administration in relation to oestriadiol, or the dose of progesterone used. The timing of progesterone administration is crucial, because the action on LH release may prove inhibitory when progesterone is given before or simultaneously with oestriadiol in women (Leyendecker et al., 1976; March et al., 1979) and in intact rhesus monkeys (Helmond et al., 1981). The dose of progesterone is also relevant in primates, because in contrast to the facilitating effect of low circulating concentrations, a high concentration of the steroid proved inhibitory (Helmond et al., 1981).

Menopause might also have a modulating role. The preovulatory discharge of LH in response to stimulation with oestriadiol and progesterone is a late acquisition during puberty, requiring a certain level of ovarian activity. Additionally, menopausal women are older, and age-related changes, with influence on the reproductive and other endocrine areas, have been described in the central nervous system of distinct mammalian species and the human (Wise, 1989). Recent studies have confirmed that menopausal women may respond with LH surges to adequate oestrogen stimulation, and that the response is potentiated by progesterone (Karande et al., 1994; Cano and Aliaga, 1995). The fact that the LH surges were elicited, however, does not negate the possibility that the performance of that function may be affected by menopause. In the present study, we investigated the effect of varying doses of progesterone after distinct concentrations of circulating oestriadiol in two different populations, represented by premenopausal and postmenopausal women. Our purpose was to...
discern whether age and menopausal status affect the oestradiol threshold required for a positive LH response to progesterone or the magnitude of the LH surge.

Materials and methods

Patients

Twenty-nine healthy women volunteered initially for the study. The medical history and the physical examination, including height, weight, blood pressure, breast palpation and bimanual vaginal examination were normal in all cases. Two different groups of women were established according to age and ovarian status; the first was composed of 12 premenopausal subjects aged 20.3 ± 2.4 years, with regular menstrual cycles of 28.7 ± 1.5 days, body mass index of 21.4 ± 1.2 kg/m² (mean ± SD), and who had never taken hormones. A sample of blood obtained on day 20 of the cycle prior to stimulation showed progesterone levels >8 ng/ml, and normal values of prolactin and thyroid stimulating hormone (TSH) in all cases. The second group comprised 17 postmenopausal women, aged 51.8 ± 2.3 years, amenorrhoeic for at least 1 year, and with serum FSH levels >30 IU/l; the menopausal age was 2.4 ± 1.1 years, the body mass index 24.9 ± 1.6 kg/m² (mean ± SD), and all had arrived at menopause naturally. Informed consent was obtained in all cases in accordance with the Ethics Committee of the Hospital.

Protocol

Each volunteer received progesterone diluted in filtered and sterile olive oil intramuscularly in two successively increasing doses, over 2 consecutive days. Based on random assignment, each woman received two distinct levels of progesterone stimulation: either 10 mg progesterone on the first day, followed by 25 mg on the second, or 25 mg progesterone on the first day, followed by 50 mg on the next day. Those two different magnitude progesterone stimulation regimens were given under conditions of three different levels: low, moderate, and high, of oestrogen priming. The low, hypo-oestrogenic status was defined by day 5 of the cycle in the premenopausal group, and the untreated postmenopausal subjects. The moderate oestrogen priming condition was defined by day 9 of the cycle in premenopausal volunteers, and by the application of a 0.1 mg oestradiol patch in postmenopausal women, changed every second day, for a total of 5 days. Progesterone was then administered on days 3 and 4 of that period. Finally, both protocols of progesterone were applied on the third and fourth day of a high dose of transdermal oestradiol (four 0.1 mg oestradiol patches) in both the premenopausal (days 3–7 of the cycle) and the postmenopausal women. The premenopausal women were studied over six consecutive cycles, and the inter-stimulation intervals in the postmenopausal group were of 3 weeks. Both patches and progesterone injections were always administered at 0900 h.

Blood and urine collection

Blood samples were obtained from a forearm vein. The extraction protocol included a daily sample obtained at 0900 h for 2 days, before stimulation with progesterone. On the next day, the first dose of progesterone was injected immediately after obtaining a third basal sample. Then, a total of three additional samples, separated by 2 h intervals, was collected. On the following day, another sample was taken at 0900 h, and then the second dose of progesterone was injected. The same extraction protocol, three more samples separated by 2 h intervals, was employed. One sample was subsequently taken at 0900 h for 1 more day. The blood was permitted to clot at room temperature, and the serum separated and stored at –40°C until assay.

Urine was collected on each day in which blood samples were obtained for each protocol. Women were instructed to collect the total urine produced during 24 h, and store it in three different containers, corresponding to 8 h fractions. The first fraction started at 0800 h. The three fractions of the day were kept refrigerated until their delivery to the hospital the next morning. The urine volume of each fraction was measured, and aliquots were obtained. After measuring the concentration of LH per aliquot, the value was multiplied by the volume of the fraction to obtain the total amount of the hormone excreted in that 8 h period, which was referred to as total LH.

An LH surge in response to progesterone was defined for serum as a sustained level (two or more concurrent values) twice the mean of the three baseline values, obtained before the first injection of progesterone. For the urine, the same criterion was referred to the mean of the six 8 h urine fractions collected during the 2 days prior to progesterone administration, and a surge was defined only if one single fraction attained the double of that value. The peak was defined as the highest LH value, and the increment, expressed both as absolute values and as percentage, as the height of the LH peak over baseline values. The area under the surge (AUS) of LH was calculated from the geometric area defined by the start and the end of the surge in urine, while in serum it was calculated from the same magnitude referred to the four time-points available at each day of progesterone stimulation.

Hormone assays

All samples from each individual were analysed in duplicate by radioimmunoassay in the same assay. LH was measured with a commercial system (BioMérieux, Marcy-L’Étoile), which used a double monoclonal antibody technique, where the first antibody was coated on the assay tube wall and the second was labelled with 125I. The immunological reaction of each antibody led to the formation of the complex first antibody–LH–[125I]second antibody on the assay tube wall. The detection limit of the assay was 0.4 IU/l, and the reference standard employed was calibrated to the first IRP MRC 68/40. The intra- and inter-assay variations were always below 6% at three distinct LH concentrations corresponding to the low, medium, and high areas of the standard curve.

The measurements of progesterone and oestradiol were also made with RIA (Bio-Mérieux), where the corresponding steroid, either progesterone or oestradiol, in the sample competed with a fixed amount of the same 125I-labelled steroid for a number of specific anti-steroid antibodies coated on the inner wall of the tube. The intra- and inter-assay variation of the assays were always <11%.

Statistics

Analysis of variance for repeated measurements was used to detect differences in the level of oestradiol attained by each group of women at the low, moderate and high level of oestradiol priming. The non-parametric Mann–Whitney U-test was used to compare results obtained with each progesterone protocol for distinct parameters of the LH response within groups, and to test eventual differences between both groups. Statistical analysis was performed with the Minitab statistical package (Minitab Inc., PA, USA). Significance was defined as P < 0.05.

Results

Only 24 volunteers were included in the final analysis of the data, since five women (two premenopausal and three postmenopausal) failed to complete the study.
Table I. Oestradiol concentrations (pg/ml, mean ± SD) attained by both postmenopausal and premenopausal women during the 5 days of the study for the distinct levels of oestradiol priming (low, moderate, high). Progesterone was added on days 3 and 4 of each protocol. Indications regarding the dose of transdermal oestradiol applied, or the range of days of the cycle considered in the premenopausal group, appear in parentheses.

<table>
<thead>
<tr>
<th>Days</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal Low (untreated women)</td>
<td>20.7 ± 10.3</td>
<td>19.6 ± 8.7</td>
<td>22.7 ± 12.0</td>
<td>19.4 ± 10.7</td>
<td>17.6 ± 8.6</td>
</tr>
<tr>
<td>Moderate (0.1 mg oestradiol)</td>
<td>16.8 ± 8.6</td>
<td>80.1 ± 15.2</td>
<td>79.5 ± 9.7</td>
<td>78.7 ± 7.5</td>
<td>74.2 ± 10.1</td>
</tr>
<tr>
<td>High (0.4 mg oestradiol)</td>
<td>23.5 ± 10.0</td>
<td>282.5 ± 57.5</td>
<td>285.5 ± 54.0</td>
<td>313.0 ± 84.0</td>
<td>274.0 ± 95.5</td>
</tr>
<tr>
<td>Premenopausal Low (days of cycle 3–7)</td>
<td>34.5 ± 7.9</td>
<td>37.0 ± 10.7</td>
<td>43.5 ± 10.7</td>
<td>38.9 ± 9.5</td>
<td>34.7 ± 7.5</td>
</tr>
<tr>
<td>Moderate (days of cycle 7–11)</td>
<td>57.4 ± 8.7</td>
<td>65.0 ± 10.9</td>
<td>74.4 ± 14.6</td>
<td>64.4 ± 14.4</td>
<td>52.2 ± 13.3</td>
</tr>
<tr>
<td>High (0.4 mg oestradiol)</td>
<td>36.0 ± 6.0</td>
<td>297.5 ± 84.5</td>
<td>267.4 ± 71.5</td>
<td>314.1 ± 44.3</td>
<td>277.6 ± 75.0</td>
</tr>
</tbody>
</table>

**Serum oestradiol and progesterone levels**

The serum oestradiol levels (mean ± SD) obtained in each group, after averaging the two cycles studied with each level of oestradiol priming, are shown in Table I. A clear hierarchy in oestradiol stimulation was accomplished, ranging from the pure hypogonadic women, represented by the untreated postmenopausal women, to the higher oestradiol concentration obtained in women stimulated with 0.4 mg of transdermal oestradiol. Untreated premenopausal women on days 5 and 9 underwent slight decreases in their oestradiol levels following progesterone injections. The analysis of variance for repeated measurements detected differences in the level of oestradiol between the postmenopausal untreated women and day 5 controls \( (P < 0.001) \) at each of the progesterone stimulation protocols. The same level of significance was detected at the next stimulation step, represented by volunteers treated with 0.1 mg patches and premenopausals on day 9 \( (P < 0.001) \), whereas no difference was found between either group when stimulated with four 0.1 mg oestradiol patches.

The progesterone concentration (mean ± SD) achieved by each of the double-stimulus protocols employed is represented in Figure 1. In both cases, the levels attained in serum by the steroid increased on the second day, thus mimicking better the physiological behaviour of progesterone after ovulation. There were no differences in the level of progesterone between the premenopausal and postmenopausal women or when, not shown in the figure, volunteers were grouped according to their oestradiol status.

**Serum and urine LH response**

The detection of pituitary LH surges was restricted to the protocols using four 0.1 mg oestradiol patches in either group. The positive response was observed in both serum and urine. When individual cases were analysed, a surge of LH in serum was detected in 12 out of the 14 postmenopausal cases stimulated with 10/25 mg progesterone, and in eight out of 14 of those stimulated with 25/50 mg progesterone. In the premenopausal group, a surge of LH was detected in nine out of the 10 women for both progesterone stimulation dosages. The rate of women obtaining LH surges was slightly higher when urine was considered, since they were observed in 13 and 12 of the 14 postmenopausal women for the 10/25 and 25/50 mg progesterone respectively, and in all the 10 premenopausal subjects. Figure 2 shows the representative LH profiles obtained in serum and urine from one woman from each group.

At the lower levels of oestradiol stimulation, only small
increases of LH were occasionally detected with the two progesterone protocols, particularly in the premenopausal women on day 9. Those increases were clearer in the morning following the first progesterone dose, just before administration of the second dose of steroid.

The serum concentration of LH and the urine levels of total LH (mean ± SD) obtained at each step of oestradiol priming are represented in Figure 3. Since no statistical difference was detected when data obtained in each subject with each progesterone protocol were compared, the LH values obtained for serum and urine with both progesterone protocols were pooled together. The figures employed for the obtaining of the values in the figure, therefore, were the mean of the results found in each volunteer for each progesterone dose. The baseline serum LH concentrations (mean ± SD) achieved in the premenopausal volunteers (5.9 ± 2.0 IU/l on day 5, and 6.5 ± 3.4 IU/l on day 9) were substantially lower than the corresponding values in the untreated postmenopausal women (67.6 ± 15.1 IU/l). Differences between pre- and postmenopausal women were also clearly delineated in urine, where the baseline values (mean ± SD) obtained for total LH in premenopausal women, 0.7 ± 0.4 IU on day 5, and 0.7 ± 0.3 IU on day 9, were clearly lower than the 5.1 ± 2.1 IU measured in postmenopausal patients.

Table II includes parameters in serum and urine that compare the rapidity and magnitude of the responses of LH in pre- and postmenopausal women. The onset of the LH surge, defined by the first time-point (or 8 h fraction in the case of urinary LH) included in the detected surge, occurred soon after the administration of progesterone in both groups. As a result, most of the time-points included in the surge accumulated on the first day of progesterone administration. Some women (three and one premenopausal, under 10/25 mg progesterone and 25/50 mg progesterone, respectively, and two postmenopausal under 10/25 mg progesterone) had an advanced surge, detected in serum and urine, initiated in all the cases on the day before the 10/25 mg progesterone administration. The differences found for the AUS between women of each group in serum and urine were not discernible relative to the dose of progesterone administration. In contrast, differences between groups were substantial for the 10/25 mg progesterone protocol, especially in urine. Those differences were significant in serum \((P < 0.03)\), and accumulated on the first day, with postmenopausal women producing higher LH responses. In urine, differences were significant on both days of progesterone stimulation \((P < 0.005)\). Again, Table II confirms the differ-

**Figure 2.** Representative luteinizing hormone (LH) profiles obtained in serum and urine for two women, one postmenopausal and the other premenopausal. The dose of progesterone used was 10 mg on day 3 and 25 mg on day 4.

**Figure 3.** Serum concentration of luteinizing hormone (LH) (upper panel) and urine levels of total LH (lower panel) (mean ± SD) obtained for low (left), medium (centre), and high (right) levels of oestadiol priming. Since no statistical difference was detected when data obtained in each subject with each progesterone protocol were compared, the LH values obtained for serum and urine with both progesterone protocols have been pooled together at each oestadiol priming level. The low (both groups of women) and the moderate (only premenopausal) levels of oestrogen priming were achieved with endogenous oestrogens only, where days 5 (low) and 9 (moderate) of the cycle represented the days in which the first progesterone dose was administered to premenopausal women. Closed circles: postmenopausal women. Open circles: premenopausal women. Note that the scales of the vertical axis in both panels are logarithmic.
ences after comparing mean values from both progesterone protocols. The increment of LH was of the same magnitude when both progesterone stimulation protocols were compared within each group. However, the amplitude of the surge was higher in the postmenopausal group in serum and urine. The difference was detected when the comparison was established between data obtained with the same stimulation dose of progesterone, either 10/25 mg ($P < 0.001$ in serum and in urine) or 25/50 mg ($P < 0.03$ in serum and $P < 0.005$ in urine) or when, as Table II shows, the mean data from both progesterone protocols were compared. In contrast, premenopausal women yielded higher percentage increases of LH when compared with baseline. This was also confirmed for data obtained with the same stimulation dose of progesterone ($P < 0.001$ in serum and $P < 0.02$ in urine for 10/25 mg progesterone, and $P < 0.005$ in serum and $P < 0.05$ in urine for 25/50 mg progesterone) and for mean values (Table II). Finally, the peak LH urine level was higher in postmenopausal women, when either each progesterone protocol was considered ($P < 0.001$), or when the comparison was established between the mean values of both protocols (Table II).

Discussion

Previous studies have confirmed that the type and magnitude of LH response depend upon the dose and duration of oestrogen administration, and that the addition of small amounts of progesterone after oestradiol augments and advances the positive LH response (Hotchkiss and Knobil, 1996). There is also information about the minimum dose and time of oestrogenic stimulation required to produce a significant increase in LH (Young and Jaffe, 1976). How that threshold may be affected by the addition of progesterone is largely unknown. It is also unknown whether menopause modulates that progesterone action. In this context, we have designed a two-step progesterone stimulation which, although not exactly concordant (Hoff et al., 1983), keeps some similitude with the natural progesterone increase in the early luteal phase.

In addition to serum, we have used urine to measure LH, since in our hands urinary LH reflects with high sensitivity and short delay the LH surges in serum (Cano and Aliaga, 1995). The urine data are particularly relevant, since they provide information on the LH surges obtained with each protocol, which might be fragmentary with the interruption of serum sampling 6 h after each progesterone injection. In this study, urinary LH values have confirmed the findings in serum that, due to the fast response of LH to progesterone, detected the significant changes of LH in the majority of the cases.

To establish the comparability of the premenopausal and postmenopausal women, the endocrine scenario in which the stimulation takes place must be very similar. The only variables that should operate are the ovary, which is active and hence the source of potentially disturbing substances in the premenopausal group, and age, which is greater in the postmenopausal women. The sex steroid levels, therefore, must be of similar range for each group at each stimulation step. This requirement compelled us to select the early follicular phase of the cycle (days 3–7), and not the peri-ovulatory days, for applying the high oestradiol stimulation to premenopausal women under conditions similar to the postmenopausal group. The analyses of variance detected differences in both the level of oestradiol and the rate of increase at the first and second stimulation steps, with higher stimulation for the premenopausal group. It is unlikely, however, that those differences might be relevant, since the LH surges were detected only at the highest oestradiol stimulation level, after application of four 0.1 mg oestradiol patches, when the oestrogenic milieu was similar in both groups. At the lower levels of oestradiol stimulation, only small increases of LH were occasionally detected with the two progesterone protocols, particularly in the morning after the first progesterone dose. This phenomenon may result from the diurnal rhythm of LH, that begins between 0600 and 1200 h in urine (Edwards, 1980).

The fact that the oestradiol threshold for progesterone stimulation was similar in both groups suggests that neither older age nor the chronic deprivation of ovarian function affects seriously the ability of the hypothalamic–pituitary unit to produce an LH surge if an adequate stimulation is received. Studies in rats have shown that age is an important variable affecting the functionality of the central nervous system areas involved in reproduction (Finch et al., 1984; Wise, 1989). Although this possibility cannot be discarded in humans, it is perhaps relevant only at an age older than that of our group, which consists of recent postmenopausal women. The

Table II. Values (mean ± SD) obtained in serum and urine for distinct parameters related to the LH surge in postmenopausal and premenopausal women.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Serum</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Onset (h)</td>
<td>AUS day 3</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>2.6 ± 0.9</td>
<td>95.6 ± 48.7</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>2.5 ± 1.1</td>
<td>186.2 ± 154.4</td>
</tr>
</tbody>
</table>

*P < 0.02, *P < 0.002, *P < 0.0001, *P < 0.04, *P < 0.005.

AUS = area under the surge.
menopausal status, i.e. the ovarian factor, also does not seem to determine clear differences between both groups, at least on the days of the cycle selected for the premenopausal women. However, it must be underlined again that the recent occurrence of menopause in our women means that a residual ovarian contribution cannot be absolutely discarded. The weight of the ovarian factor derives from the possible influence of steroids other than oestradiol and progesterone, and peptides of ovarian origin. In fact, there is increased secretion of peptides such as inhibin around day 8–9 of the cycle (Groome et al., 1994), and a recent study has shown that the administration of only oestradiol and progesterone in the early follicular phase to premenopausal women is insufficient to reproduce a gonadotrophin surge of the same magnitude as in the normal menstrual cycle (Taylor et al., 1995). In our model, the magnitude of the LH response in the normal menstrual cycle was not included in the comparison, and therefore it is possible that the LH surges detected in the young, premenopausal women might be sub-optimal. The study of hormonal dynamics at mid-cycle confirms, actually, that the mean duration of the LH surge attains 48 h (Hoff et al., 1983), a duration exceeding that of our LH-induced surges.

In addition to the influence of gonadal peptides, other factors with regulatory effect on the expression of gonadotrophin subunit genes by the gonadotrophs are GnRH and oestradiol (Evans et al., 1996). The fact that a high output of GnRH to the gonadotrophs is conceivable in our postmenopausal women might contribute to the high amplitude of the LH surges in that group.

The facilitatory action of oestradiol on the GnRH-stimulated secretion of LH has been well established for both immunoreactive and bioactive forms of the hormone (Urban et al., 1991; Quyyumi et al., 1993). The level of oestrogen priming, i.e. the dose and duration of oestrogen required, is unclear. In one study (Karande et al., 1994), the simultaneous administration of 0.2 mg transdermal oestradiol with progesterone, after preparation with 0.05 mg oestradiol patches, produced an LH surge in five out of nine postmenopausal women. In our hands, the positive response of LH was obtained only when progesterone was administered subsequently to the high oestradiol level provided by four 0.1 mg patches. It is possible, therefore, that the threshold for the response of LH in postmenopausal women resides around the level of stimulation provided by 0.2 mg transdermal oestradiol, when operating under the above-mentioned experimental conditions. It remains to be seen whether the subsequent, instead of simultaneous, addition of progesterone improves the efficacy of the stimulus, and whether that threshold applies also to premenopausal women.

Finally, the mechanism of that facilitatory effect of progesterone is still unclear. The role of the pituitary has been clearly defined by the hypophysiotropic clamp model, where pituitary function is controlled by exogenous GnRH (Karsch, 1987). More recently, a study using 100 mg/day of the progesterone antagonist mifepristone during the first half of the follicular phase showed a significant attenuation in LH and follicle stimulating hormone (FSH) response to GnRH (Kazem et al., 1996). The possible implication of the hypothalamic LH surges induced by oestradiol and progesterone antagonists supress both spontaneous (Dubourdieu et al., 1994) and steroid-induced (Kolp et al., 1992) LH surges. This is in spite of the unchanging GnRH mRNA levels (Petersen et al., 1995) and, although subjected to debate, GnRH pulse frequency (Adams et al., 1994) during the surge. Therefore, both hypothalamus and pituitary seem to be involved in the process, with their relative roles still not completely delineated.

In conclusion, under the experimental conditions of our study, we have found that the administration of progesterone induced LH surges after an adequate oestrogenic preparation both in young premenopausal and in older postmenopausal women. The magnitude of the LH response was higher in the postmenopausal group, but the relative increase above baseline was higher in the premenopausal subjects. In both types of women, progesterone was unable to rescue LH surges when oestradiol levels decreased at a concentration similar to day 9 of the cycle. Finally, a 10 mg i.m. progesterone injection sufficed to accomplish that action, while higher levels failed to magnify the effect, thus discounting a dose–response effect of the steroid.

Acknowledgement
This work was supported by grant 93/0680 from Fondo de Investigaciones Sanitarias, Madrid, Spain.

References


Karsch, F.J. (1987) Central actions of ovarian steroids in the feedback


Received on September 24, 1997; accepted on December 12, 1997