Arch. Gynäk. 221, 29–45 (1976)

Archiv für
Gynäkologie

Experimental Studies on the Positive Feedback Effect of Progesterone, 17α-Hydroxyprogesterone and 20α-Dihydroprogesterone on the Pituitary Release of LH and FSH in the Human Female

The Estrogen Priming of the Progesterone Feedback on Pituitary Gonadotropins in the Eugonadal Woman*

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Untersuchungen zur positiven Rückkopplung von Progesteron, 17α-Hydroxyprogesteron und 20α-Dihydroprogesteron auf die hypophysäre Sekretion von LH und FSH bei der Frau

Summary. Administration of progesterone eugonadal women during the mid follicular phase of the menstrual cycle failed to induce a postive feedback effect on the serum concentrations of LH and FSH. The levels of estradiol in serum decreased following the injection of progesterone without a parallel change in LH and FSH concentrations indicating a direct ovarian effect of the exogenous progesterone.

In the late follicular phase of the cycle, when preovulatory levels of estradiol were present in serum, or under a ethinyl estradiol treatment progesterone was able to induce an LH discharge indicating the requirement of an estradiol priming of the positive feedback of progesterone in eugonadal women.

In order to establish the time required for a sufficient estrogen priming with preovulatory levels of estradiol in serum 3 mg of estradiol-benzoate were administered i.m. 1, 12 and 24 h prior to the administration of 30 mg of microcristalline progesterone in the midfollicular phase of the menstrual cycle, when progesterone alone did not cause an LH surge. Only when estradiol-benzoate was injected 24 h prior to the progesterone administration an LH surge reproducible in time course and magnitude occurred. Administration of estradiol-benzoate alone under these conditions did not cause an LH surge within the elapse of time after the injection when the progesterone induced LH surge occurred. Thus, these experiments demonstrate that a defined estrogen priming is required for the positive feedback effect of progesterone on the gonadotropin release in eugonadal women.

Furthermore, progesterone levels in serum of about only 1–2 ng/ml were required for the induction of an LH surge indicating that under physiological

* Supported by grants of the Deutsche Forschungsgemeinschaft (No. 67/1; 67/3; 67/5)

** Postdoctoral fellow; supported by the Deutsche Forschungsgemeinschaft

conditions progesterone may have an supplementory effect on the primarily estradiol induced LH midcycle peak.

17-hydroxyprogesterone administered during the mid follicular phase of the menstrual cycle and under pretreatment with ethinyl estradiol failed to induce a positive feedback effect on the serum concentrations of LH and FSH, indicating that this steroid does not play a regulatory role on the midcycle LH release in women.

20α-dihydroprogesterone administered under the same experimental conditions as 17-hydroxyprogesterone seems to be able to induce an LH surge in serum provided there is an adequate estrogen priming.

Zusammenfassung. Durch die Gabe von Progesteron während der mittleren Proliferationsphase des menstrualen Cyclus konnten keine LH-Ausschüttungen aus der Hypophyse hervorgerufen werden. Statt dessen kam es zu einem graduellen Abfall von Östradiol im Serum — ohne eine Veränderung der Gonadotropinspiegel im Serum —, was darauf hinweist, daß Progesteron einen direkten Einfluß auf die ovarielle Östradiolbiogenese hat.

In der späten Proliferationsphase oder in der mittleren Proliferationsphase, bei gleichzeitiger Gabe von Äthinyl-Östradiol, führte die Gabe von Progesteron zu einer positiven Feedback-Reaktion auf die hypophysäre Gonadotropinsekretion. Das aus diesen Beobachtungen ableitbare Östrogen-"Priming" der positiven Feedback-Reaktion von Progesteron während des normalen Cyclus wurde in weiteren Untersuchungen analysiert:

In verschiedenen Untersuchungsreihen wurden 3 mg Östradiol-Benzoat 1, 12 und 24 Std vor der Gabe von 30 mg Progesteron i.m. injiziert. Nur bei einem Abstand von 24 Std zwischen den Injektionen wurde ein reproduzierbarer Anstieg von LH und FSH beobachtet. Die Gabe von Östradiol-Benzoat alleine führte nicht zu LH-Ausschüttungen in dem Zeitraum, in welchem sie unter zusätzlicher Gabe von Progesteron beobachtet wurden.

Diese Ergebnisse zeigen, daß die positive Rückkopplungsreaktion von Progesteron auf die hypophysäre Sekretion von LH und FSH ein definiertes Östrogen-"Priming" benötigt. Außerdem konnte gezeigt werden, daß Progesteronkonzentrationen im Serum im Bereich von 1—2 ng/ml ausreichten, um eine LH-Ausschüttung zu induzieren. Diese Beobachtung steht mit der Vorstellung im Einklang, daß Progesteron einen synergistischen Beitrag bei der primär östradiol-induzierten LH-Ausschüttung in Cyclusmitte leistet.

17-Hydroxyprogesteron war nicht in der Lage, eine LH-Ausschüttung zu induzieren. Diese Beobachtung spricht gegen die Auffassung, daß dieses Steroid an der Regulation der LH-Ausschüttung in Cyclusmitte beteiligt ist. Unter Vorbehandlung mit Äthinyl-Östradiol konnte durch die Gabe von 20α-Dihydroprogesteron ein LH-Gipfel im Serum induziert werden.

In a recent publication it was suggested (Leyendecker et al., 1972a) that progesterone might play an additional role in the regulation of the primarily estradiol induced midcycle LH peak in the human female. In the present study the attempt is made to provide further experimental evidence to support this hypothesis.

17-hydroxyprogesterone (17-OHP) and 20α-dihydroprogesterone (20-DHP) —

closely related to progesterone – are two other ovarian steroids which change their serum concentrations during the periovulatory phase of the human menstrual cycle (Ross et al., 1970; Abraham et al., 1972; Thorneycroft et al., 1974; Wu et al., 1974; Leyendecker et al., 1975b). 17-OHP has been considered to be additionally involved in the regulation of the LH midcycle discharge (Vande Wiele et al., 1970; Abraham et al., 1972). 20-DHP has been shown to be able to induce a positive feedback effect on the LH secretion in the rodent (Swerdloff et al., 1972). We are not aware of analogous experiments in the human. This prompted us to study whether these steroids – in addition to progesterone – would exert an effect on the abrupt release of LH and FSH in the human female.

Materials and Methods

Except for one person, W.S., 23 years of age, with gonadal dysgenesis, the studies were performed in eugonadal volonteers with histories of regular cycles and normal biphasic temperature patterns in control cycles.

Progesterone was administered i.m. or by continuous i.v. infusion at various stages of the proliferative phase of the menstrual cycle alone or in combination with oral pretreatment with 60 μg of ethinyl estradiol (Progynon C®, Schering A.G., Berlin) per day or parenteral pretreatment with a single i.m. dose of 3 mg of estradiol-benzoate (Progynon B oleosum®, Schering A.G., Berlin) 1, 12 and 24 h prior to the i.m. injection of progesterone.

The patient with gonadal dysgenesis (W.S.) received a continuous i.v. infusion of progesterone after pretreatment with 60 μg of ethinyl estradiol per day in order to suppress elevated serum levels of LH and FSH.

As controls three eugonadal women were treated only by single i.m. injections of 3 mg of estradiol-benzoate in the midfollicular phase of the menstrual cycle.

Three eugonadal women received continuous i.v. infusions of 20-DHP on the 9th to 10th day of the cycle and two other received i.m. injections of 20-DHP on the 7th and 8th day of the cycle during daily pretraetment with 60 μg of ethinyl estradiol.

One eugonadal volonteer received continuous i.v. infusions of 17-OHP starting on the 9th day after onset of the menses in two different cycles. Two other eugonadal volonteers were treated with i.m. injections of 17-OHP under pretreatment with ethinyl estradiol.

In all experiments with ethinyl estradiol pretreatment the administration of this estrogen started 7 days prior to the administration of progesterone, 20-DHP or 17-OHP.

For i.m. application 30 mg of microcrystalline progesterone were used (Lutocyclin M®, Ciba A.G., Basle). For the i.v. route progesterone, 17-OHP (Merck, A.G., Darmstadt) and 20-DHP (Ikapharm, Israel) were dissolved in propylene glycol, sterilized by filtration and further dissolved in human serum albumin and normal saline.

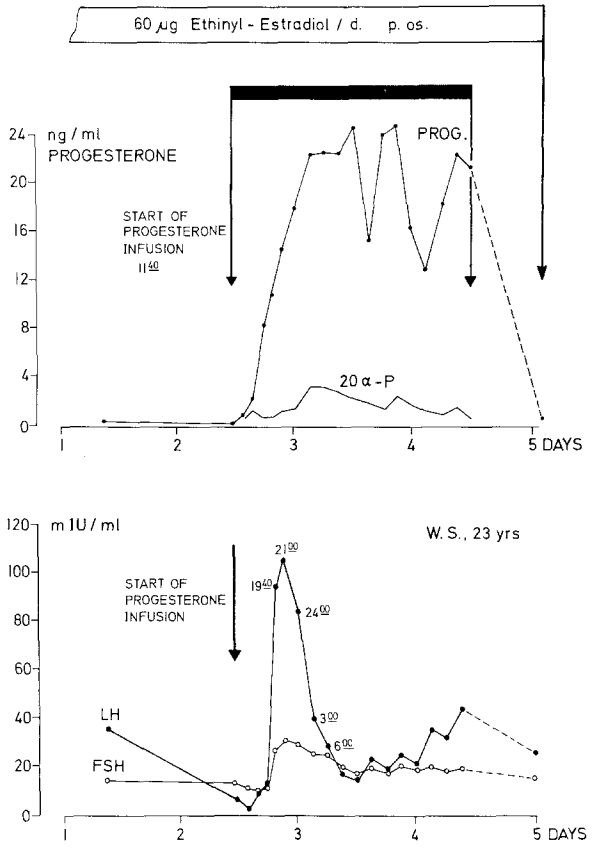
For i.m. injection of 17-OHP and 20-DHP these steroids were dissolved (10 : 1; w : v) in a castor-oil: benzyl-benzoate solution (4 : 6; v : v) and sterilized by filtration.

LH and FSH serum concentrations were measured by radioimmunoassay[1] using dioxane for separation of antibody bound and free hormones (Thomas and Ferin, 1968; Leyendecker et al., 1971). Serum concentrations of 17β-estradiol, progesterone, 17-OHP and 20-DHP were measured by radioimmunoassay (Leyendecker et al., 1972b). Separation of cross reacting steroids was achieved by celite chromatography (Korenman et al., 1970), using a *modified system* (Leyendecker et al., 1975) which allowed the simultanous measurement of these steroids in one sample of serum.

Results

Intravenous infusion of progesterone at a rate of 20 mg/24 h over a period of 48 h resulted in a prompt increase of serum progesterone to high levels within a few hours

[1] Immunochemicals were generously supplied by the National Institutes of Health (Bethesda, Maryland) and the Medical Research Council (London)


60 µg Ethinyl - Estradiol / d. p. os.
ng / ml
PROGESTERONE
PROG.
START OF
PROGESTERONE
INFUSION
11 40
20 α - P
5 DAYS
m IU / ml
W. S., 23 yrs
START OF
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INFUSION
LH
FSH
5 DAYS

Fig. 1

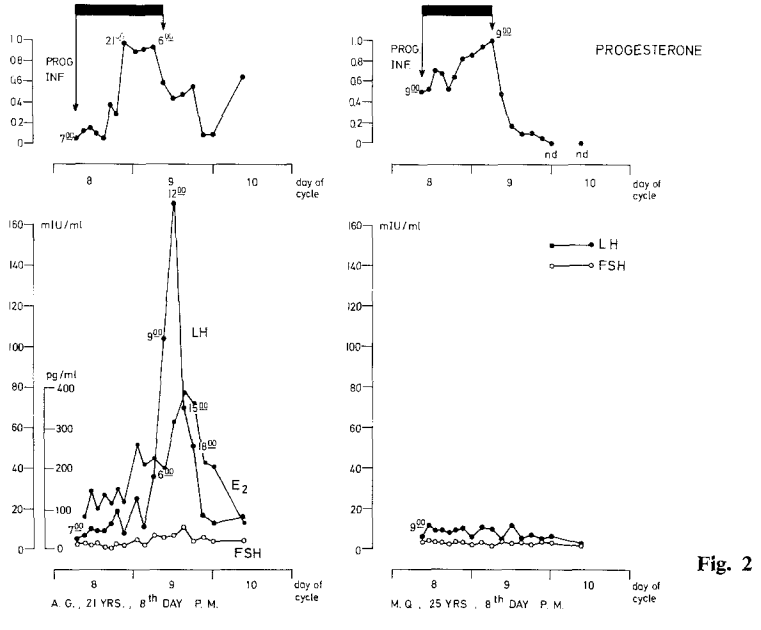
PROG
INF
PROGESTERONE
nd
day of cycle
mIU/ml
LH
FSH
pg/ml
E2
A. G., 21 YRS., 8th DAY P. M.
M. Q., 25 YRS., 8th DAY P. M.

Fig. 2

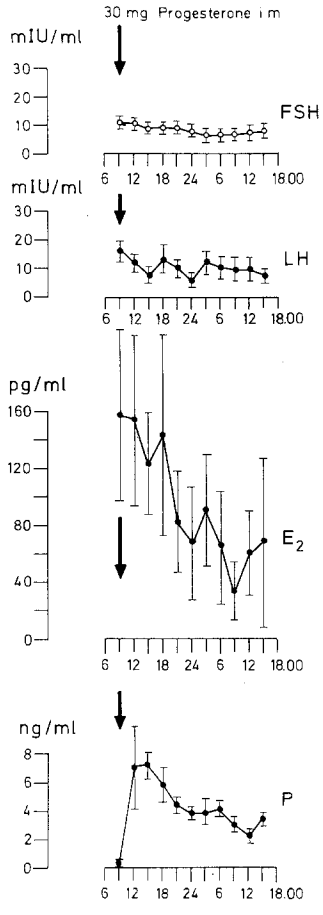

Fig. 3. The serum concentrations of FSH, LH, estradiol and progesterone after i.m. administration of 30 mg of microcrystalline progesterone during the mid follicular phase of the menstrual cycle in three eugonadal women. Means ± SEM

in a 23 years old woman with gonadal dysgenesis whose elevated serum concentrations of LH and FSH had been depressed by oral administration of 60 μg of ethinyl estradiol daily throughout the experiment (Fig. 1). Eight hours after the start of the progesterone infusion there was a first significant rise of serum LH and to a lesser extent of serum FSH. The LH and FSH concentrations returned to base line levels within 24 h after the start of the infusion.

With a reduced infusion rate in the range of 3–5 mg/24 h progesterone concentrations in serum in the range of 1.0 ng/ml could be obtained in two eugonadal women on their 8th day of the menstrual cycle (Fig. 2). In one woman a sharp rise of

Fig. 1. Intravenous infusion of progesterone at a rate of 20 mg/24 h over a period of 48 h in W.S. pretreated with 60 μg of ethinyl estradiol per day. The concentrations of progesterone, 20α-dihydroprogesterone, LH and FSH in serum

Fig. 2. The serum concentrations of LH, FSH and progesterone on days 8–10 of the menstrual cycle in A.G. and M.Q. during an i.v. infusion of progesterone for 24 h at a rate of 3–5 mg/24 h. In A.G. serum estradiol was additionally measured

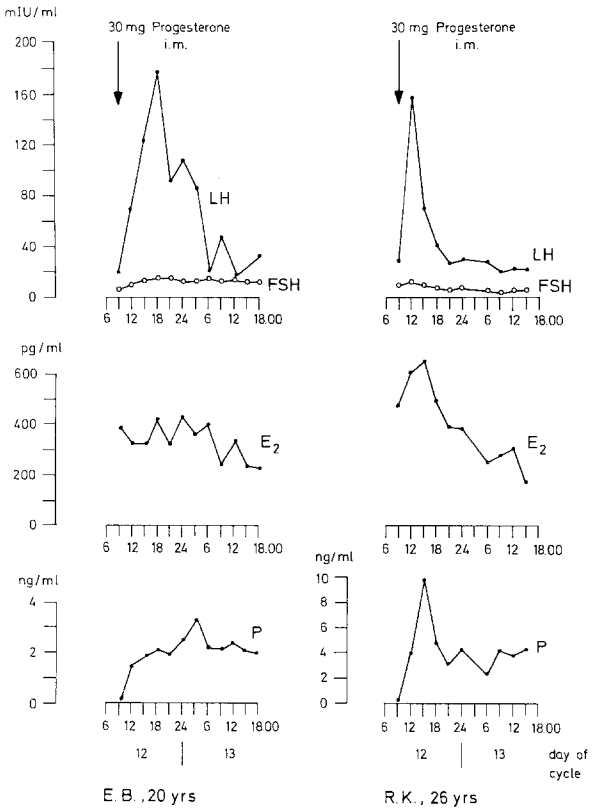

Fig. 4. The serum concentrations of LH, FSH, estradiol and progesterone on day 12 and 13 of the menstrual cycle in two eugonadal women following the i.m. injection of 30 mg of microcrystalline progesterone at 9 a.m. of day 12 of the cycle

LH was observed 24 h after the start of the infusion and approximately 9 h after the rise of progesterone in serum (the elapse of time beween the start of the infusion and the rise of progesterone in serum is due to a readjustment of the infusion rate during the experiment). LH concentrations in serum returned to base line levels within 24 h after the rise of progesterone. Prior to the LH rise the levels of serum estradiol were in the range of 100–200 pg/ml and rose up to 390 pg/ml at the end of the LH peak. In the other woman (I.Q.), however, similar concentrations of progesterone in serum did not induce a positive feedback effect on the LH secretion. Unfortunately, in this woman endogenous serum estradiol had not been determined.

In order to establish whether estradiol concentrations in serum were a critical factor for the occurrence of a positive feedback effect of progesterone on the LH release, experiments were conducted with progesterone injections at different stages of the proliferative phase of the menstrual cycle and under varying conditions of an estrogen pretreatment.

Figure 3 is a composite picture of results obtained in three women who had received i.m. injections of 30 mg of progesterone. At the time of the injections (9 a.m.) the volonteers were on their 8th, 9th and 11th day of their menstrual cycles,

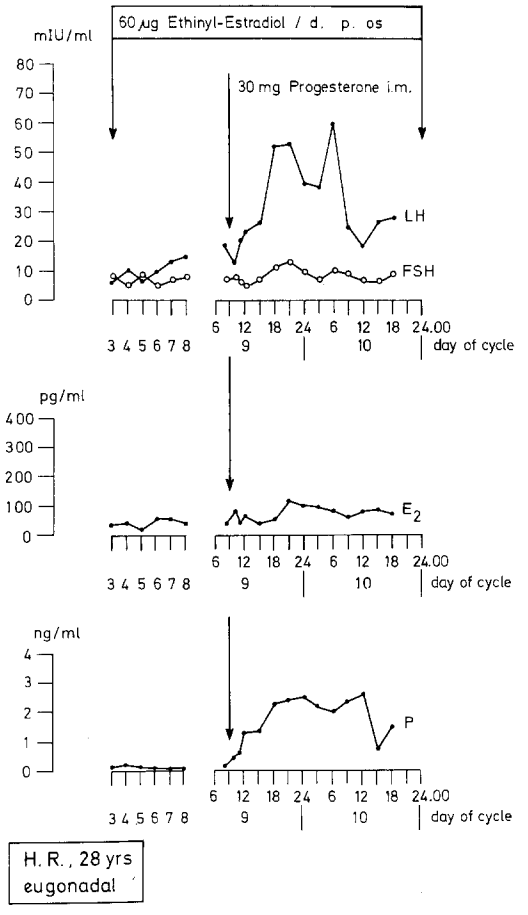

Fig. 5. The serum concentrations of LH, FSH, estradiol and progesterone during the follicular phase of the cycle in H.R. under treatment with 60 µg of ethinyl estradiol daily and following an i.m. injection of 30 mg of microcrystalline progesterone at 9 a.m. on the 9th day of the cycle

respectively. In none of these experiments the injection of progesterone was resulting in an LH increase although progesterone rose up to 7 ng/ml in serum 3 h after the injection. During the course of the experiment there was a steady fall of estradiol concentrations in serum from 160 pg/ml to less than 40 pg/ml 24 h after the injection of progesterone. This fall of estradiol levels in serum was not accompanied by a significant change of LH and FSH concentrations in serum.

When progesterone was administered in the preovulatory phase, on day 12 of the cycle (Fig. 4) in both cases studied an abrupt surge of LH in serum immediately following the injection of progesterone was observed. In E.B., the discharge had a duration of 15 h, while in R.K. the increased LH secretion lasted for only 9 h. In both women the serum levels of estradiol were in the range of 300–500 pg/ml when progesterone was injected.

Figure 5 demonstrates that injection of 30 mg of progesterone on day 9 of the menstrual cycle resulted in an abrupt LH release in a woman pretreated with ethinyl estradiol.

In order to simulate preovulatory estradiol levels in serum and in order to study their possible role in priming the positive feedback effect of progesterone on the LH

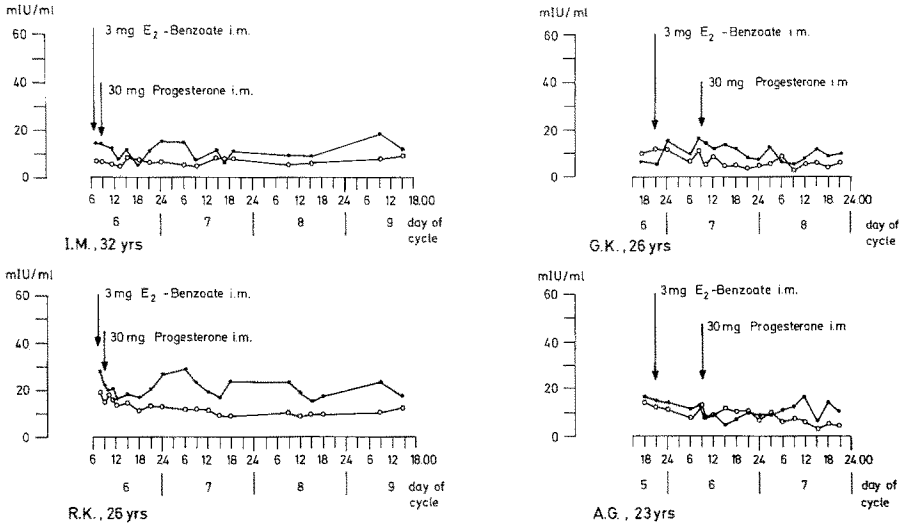

Fig. 6. The serum concentrations of LH (●——●) and FSH (○——○) during the mid follicular phase of the cycle following the i.m. injections of 3 mg of estradiol benzoate and progesterone. In pat. I.M. and R.K. the time interval between the two injections was 1 h, in Pat. G.K. and A.G. the time interval was 12 h

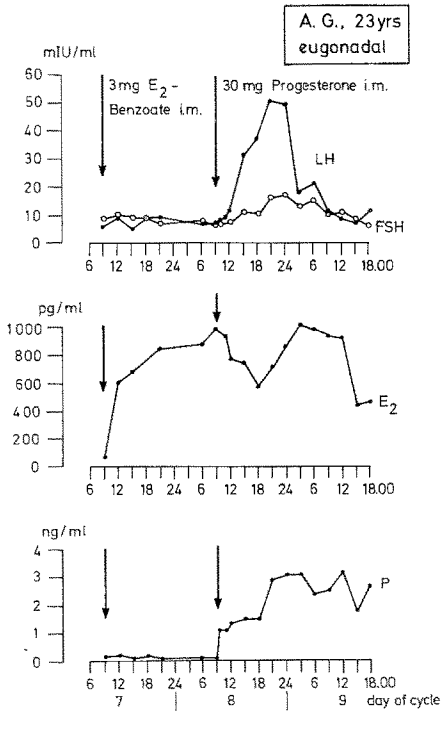

Fig. 7. The serum concentrations of LH, FSH, estradiol and progesterone during the mid follicular phase of the cycle in A.G. following the i.m. injections of 3 mg of estradiol benzoate and 30 mg of progesterone. The time interval between the two injections was 24 h

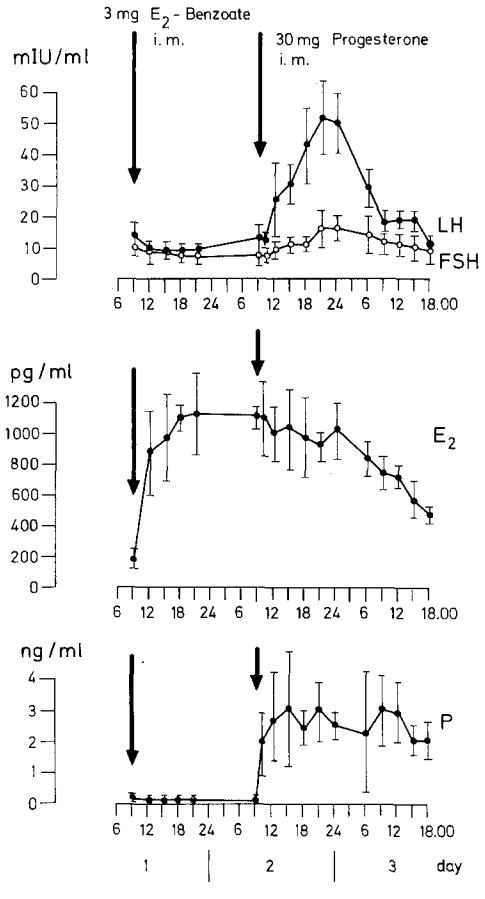

Fig. 8. The serum concentrations of LH, FSH, estradiol and progesterone during the mid follicular phase of the menstrual cycle in three women following the injections of 3 mg of estradiol benzoate and 30 mg of progesterone. The time interval between the two injections was 24 h in each woman. Means ± SEM

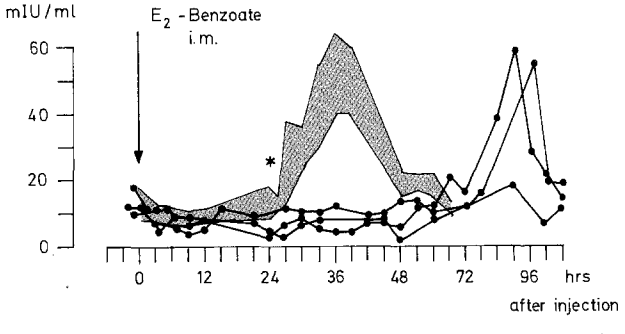

Fig. 9. The serum concentrations of LH in three women who received a single i.m. injection of 3 mg of estradiol benzoate during the midfollicular phase of the menstrual cycle (●——●) in comparison to the LH concentrations of three women (the shaded area represents the SEM range) who received an additional i.m. injection of 30 mg of progesteron 24 h after the injection of estradiol benzoate
(*) = moment of the injection of progesterone

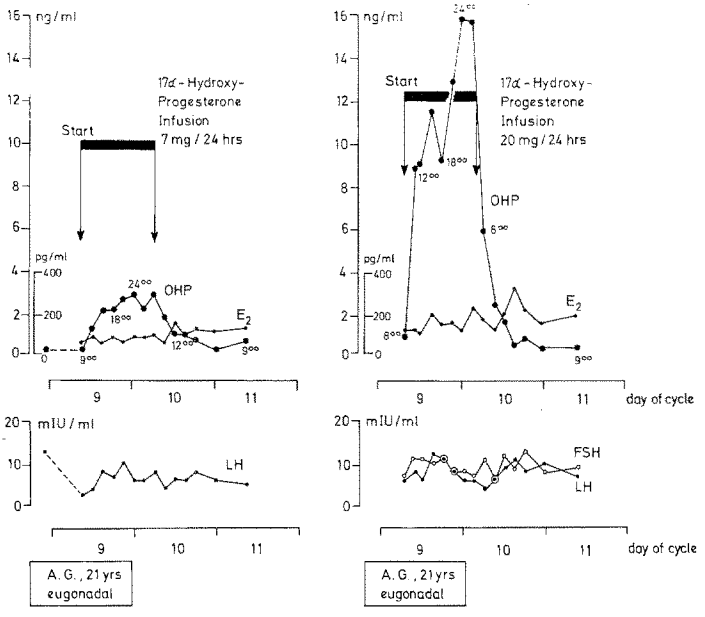

Fig. 10. The serum concentration of 17-OHP, estradiol, LH and FSH during and following the i.v. infusion of 17-OHP for 24 h at infusion rates of 7 mg and 20 mg/24 h, respectively

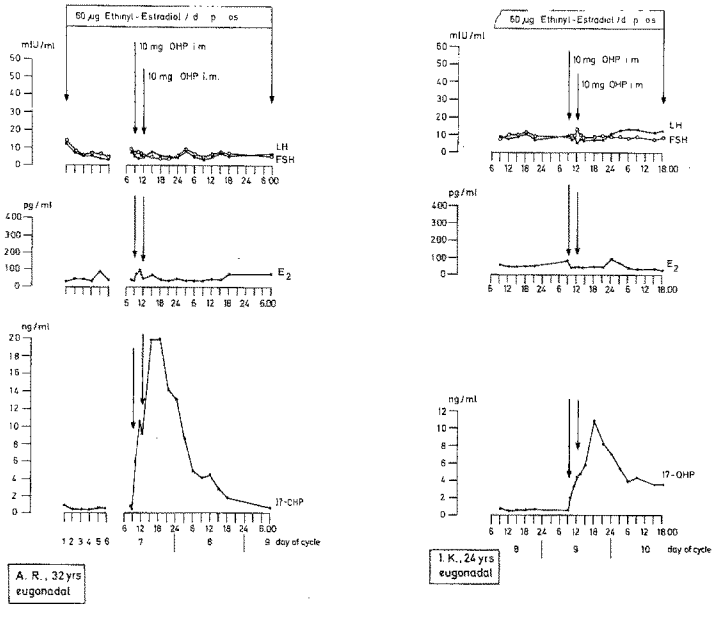

Fig. 11. The serum concentrations of LH, FSH, estradiol and 17-OHP under treatment with 60 ug of ethinyl estradiol per day and following the i.m. injection of two times 10 mg of 17-OHP

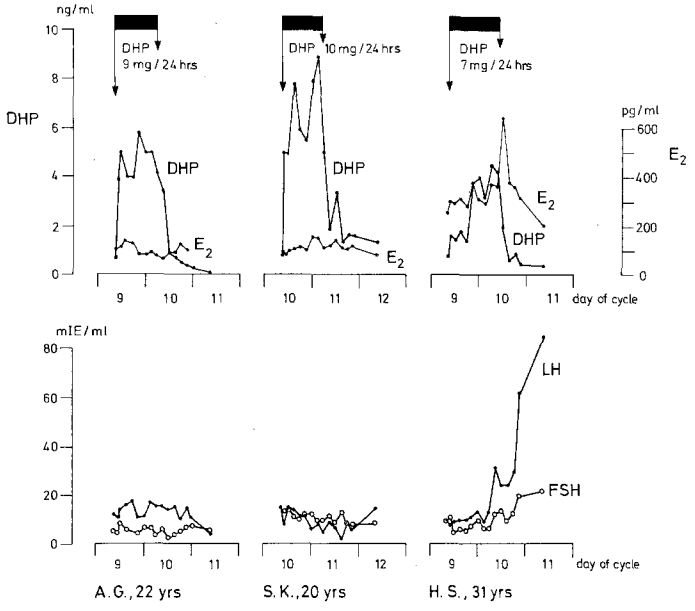

Fig. 12. The serum concentrations of 20-DHP, estradiol, LH and FSH in three eugonadal women during and following the intravenous infusion of 20-DHP for 24 h at infusion rates of 7, 9 and 10 mg/24 h, respectively

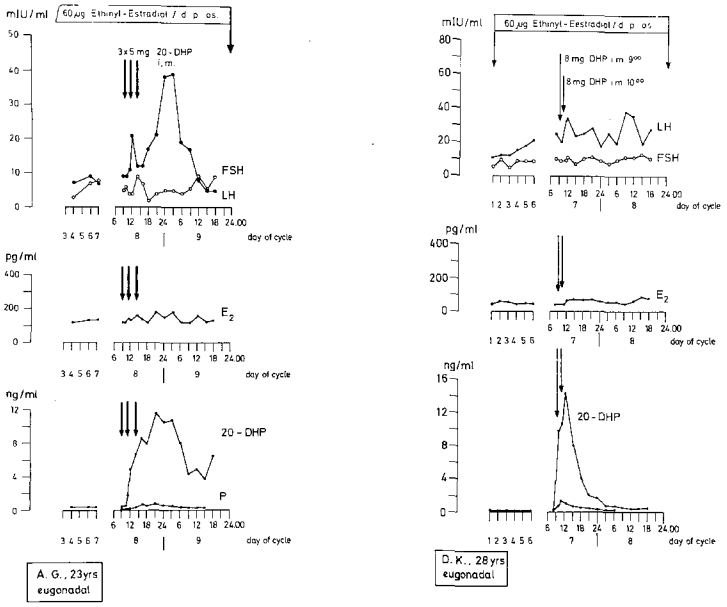

Fig. 13. The serum concentrations of LH, FSH, estradiol, 20-DHP and progesterone during treatment with 60 µg of ethinyl estradiol daily and following the i.m. injection of three times 5 mg and two times 8 mg of 20-DHP, respectively, in two eugonadal women

secretion 3 mg of estradiol benzoate were injected 1, 12 and 24 h prior to the i.m. administration of 30 mg of progesterone into women during the midfollicular phase of the cycle.

Figure 6 shows the results of the studies in which estradiol benzoate was administered one and 12 h prior to the injection of progesterone. In no case an LH surge following the injection of progesterone occurred.

When estradiol-benzoate was administered 24 h prior to the injections of progesterone (Fig. 7) the progesterone injection was followed by an abrupt release of LH and to a lesser extent of FSH with a latency phase of less than 3 h. Three experiments were performed under these conditions and in all three experiments the gonadotropin surge was reproducible and lasted for 18–24 h (Fig.8).

In a control study (Fig. 9) 3 mg of estradiol-benzoate were administered alone during the midfollicular phases of the menstrual cycle of three women. No LH peaks could be induced at the time when they had occurred in the previous (Fig. 8) experiment.

Figure 10 shows the results of i.v. infusions of 17-OHP for a period of 24 h at infusion rates of 7 and 20 mg/24 h, respectively, in one woman. The infusions were started on the 9th day of two different menstrual cycles. With an infusion rate of 7 mg/24 h a change in serum levels of 17-OHP could be obtained which was similar to the normal change observed during the periovulatory phase of the menstrual cycle. This increase of 17-OHP in serum as well as the unphysiologically sharp one during the infusion of 20 mg/24 h did not affect serum levels of LH and FSH.

The experiments were repeated under ethinyl estradiol pretreatment using i.m. administration of 17-OHP (Fig. 11). No change in serum LH and FSH could be observed following the administration of 17-OHP.

Figure 12 shows the results of i.v. infusion of 20-DHP during the mid follicular phase of three eugonadal women. No change of serum LH and FSH levels in response to the infusions of 20-DHP was observed in two women (A.G., S.K.), whose serum estradiol levels were in the range of 80–150 pg/ml during the course of the infusions. In patient H.S. serum estradiol levels were in the range of 300 pg/ml at the beginning of the infusion and were further rising reaching a peak value of 645 pg/ml. They were falling again concomitantly with a rise of serum LH and FSH, which reached preovulatory levels 48 h after the start of the infusion of 20-DHP.

Figure 13 demonstrates the effects of i.m. injections of 20-DHP in two women under pretreatment with ethinylestradiol. In one woman (A.G.) an LH peak following the injectionof 20-DHP was observed.

Discussion

The ability of progesterone to induce an abrupt release of gonadotropins from the pituitary gland in women had been demonstrated by several authors (Buchholz et al., 1964; Odell and Swerdloff, 1968; Nillius and Wide, 1971; Leyendecker et al., 1972a). The hypothesis, however, that increasing serum progesterone is the primary triggering signal for the midcycle LH release (Odell and Swerdloff, 1968) had to be rejected on the basis of newer studies on the chronological changes of the endocrine parameters during the periovulatory phase of the human menstrual cycle: The rise of

progesterone in serum is preceded by the rise of LH (Johansson and Wide, 1969; Leyendecker et al., 1972a; Abraham et al., 1972; Thorneycroft et al., 1974). Furthermore, experimental evidence has accumulated that rising estradiol-17β is the primary ovarian signal leading to the LH discharge at midcycle (Vande Wiele et al., 1970; Leyendecker et al., 1972a; Yen and Tsai, 1972; Monroe et al., 1972).

In a previous communication (Leyendecker et al., 1972a) we had suggested that progesterone may play an additional role in the regulation of the LH midcycle release through its ability to induce a positive feedback effect on the LH secretion. It is evident from the concentration of progesterone in serum during the periovulatory phase of the cycle which is rising from levels below 0.5 ng/ml to levels around 1.0 ng/ml during the course of the LH peak (Moghissi et al., 1972; Leyendecker et al., 1972a, 1975; Thorneycroft et al., 1974) that rising progesterone can only play a role in the regulation of the LH midcycle discharge if it exerts its effects a) within a short latency phase between the start of the rise of progesterone in serum and the continuing LH release at midcycle and b) at a serum concentration of around 1.0 ng/ml.

The short latency phase of the positive feedback effect of progesterone of less than 9 h had been shown in estrogen pretreated postmenopausal and castrated women (Leyendecker et al., 1972a). The present study demonstrates that in estrogen primed eugonadal women during the proliferative phase of the cycle the latency phase of the progesterone effect on the LH secretion may be even shorter (Figs. 4, 7, 8).

From Figures 2, 5 and 7 it is evident that progesterone is able to induce a positive feedback effect on the LH secretion at serum concentrations in the range of 1 to 1.5 ng/ml. This concentration is surpassed on the day of the LH peak in the normal menstrual cycle (Moghissi et al., 1972; Leyendecker et al., 1972a, 1975b).

Previous studies on the positive feedback effect of progesterone on the pituitary LH release had been performed in hypogonadal subjects (Odell and Swerdloff, 1968; Leyendecker et al., 1972a) who required estrogen pretreatment for the suppression of elevated levels of LH and FSH in serum. Due to their experimental design these studies obscured the role of estrogen in the mechanism of the positive feedback of progesterone. The data presented here show that during the midfollicular phase of the human menstrual cycle LH surges could not be induced by progesterone (Fig. 3) except for one case (Fig. 2) unless there is an adequate priming with estrogens. This priming has obviously occurred in the late follicular phase and can be artificially achieved in the midfollicular phase of the cycle by injection of estradiol benzoate 24 h prior to the injection of progesterone. Administration of estradiol-benzoate 1 or 12 h prior to the injection of progesterone did not result in a sufficient priming of the hypothalamic hypophyseal unit (Fig. 6). Thus, a defined estrogen priming is required for a positive feedback effect of progesterone on the release of gonadotropins in women.

There is no doubt that the rise of LH in serum after the injection of progesterone (Fig. 7 and 8) is due to the injection of the gestagen and not the result of the administration of estradiol-benzoate alone. In a control study estradiol-benzoate administered alone (Fig. 9) was not not able to induce LH surges at the time when they occurred following the injection of progesterone after the 24 h estradiol prim-

ing. The long latency phase and the weak response of LH in serum to an estradiol stimulus of preovulatory levels of estradiol in serum during the midfollicular phase of the menstrual cycle was also observed by others (Tsai and Yen, 1972) and contrasts with the observation of a 24–36 h latency phase between administration of estradiol-benzoate and LH surge in estrogen pretreated hypogonadal women (Leyendecker et al., 1972a) and with the observation made in the rhesus monkey (Knobil, 1974) where uniformous LH peaks can be induced with preovulatory levels of estradiol throughout the whole proliferative phase of the cycle. Presumably, in the human female, not only the progesterone positive feedback effect but also the estradiol positive feedback effect on pituitary LH secretion requires an estrogen priming (Leyendecker, 1975b) comparable with the situation in the rat estrous cycle (Kalra, 1975).

It is difficult to prove that the LH peaks shown in Figure 4 are the result of the progesterone injection and not due to the rising levels of endogenous estradiol. However, the close temporal relation to the progesterone injection, the short duration and the fact that there is no precipitous fall of estradiol in serum usually occurring during the normal LH midcycle peak are favoring the assumption that the LH peaks are a result of the progesterone injections.

The present results demonstrate that under the condition of an adequate estradiol priming progesterone is able to induce a positive feedback effect on the LH secretion at a low serum concentration in the range of 1.0 ng/ml and with a short latency phase. This supports the view that progesterone could play a role in the dosage regulation of the primarily estradiol induced LH peak at midcycle. However, it is not yet established, whether this role is an obligatory one as far as normal ovulation is concerned or constitutes only a fail safe mechanism.

In the rhesus monkey a positive feedback effect of progesterone on LH serum levels has not yet been reported (Knobil, 1974). Swerdloff et al. (1972) demonstrated that in estrogen primed female castrate rats progesterone could induce a surge of LH but not of FSH. Kalra et al. (1973) studied the effects of administration of progesterone on the levels of LH and FSH in serum during the rat estrous cycle. Progesterone was able to induce and advance the surges of LH and FSH when administered in the morning of proestrous. However, it was ineffective when given on the second day of diestrous. Considering the differences in length of the rat and human menstrual cycles the results of Kalra et al. (1973) in the rat and ours in the human female seem to correspond in that the positive feedback effect of progesterone in both rat and human female on LH and FSH levels in serum requires an adequate priming by estrogen which is accomplished in the preovulatory phase of the human menstrual cycle and in the morning of the proestrous in the rat, respectively.

It is not yet established whether the stimulatory effects of estradiol and progesterone on the gonadotropin secretion involve identical neural structures. Odell and Swerdloff (1975) claim that progestogens exhibit a facilitory effect on the LH release by lowering the threshold of estrogen stimulation of LH secretion. McCann et al. (1972) postulate that in the rat the positive feedback effects of progesterone and estradiol are related to identical neural mechanisms.

The inducability of ovulations in male castrated rats bearing an ovarian transplant by injections of progesterone but not of estradiol (Rothchild, 1966), the induction of LH peaks in individuals of testicular feminization by progesterone and not by

estradiol (Zarate et al., 1974) as well as the occurrence of an LH surge following the administration of progesterone and not of estradiol in an anorchic man (Leyendecker, 1975) at least hint at the possibility that estradiol and progesterone positive feedback mechanisms may involve different neural pathways.

Lasley et al. (1975) favor the assumption that the augmentative effect of progesterone on the LH release is mainly due to a direct effect of this steroid on the pituitary rather than due to a stimulation of endogenous LRF release. They observed an enhanced pituitary response to repeated LRF stimulations in eugonadal females pretreated with estradiol for several days when progesterone was administered 4 h prior to the first injection of LRF. Unfortunately, their experimental design obscured the observation made in this study that in estrogen primed women serum LH starts to rise without exogenous LRF stimulation round about 4 h after the administration of progesterone. Thus, the amplification effect of progesterone on the estrogen-augmented pituitary (Lasley et al., 1975) may only be partly accounted for by a direct pituitary effect.

Administration of progesterone in the mid follicular phase of the human menstrual cycle (Fig. 3) did not change serum levels of LH and FSH but resulted in a reduction of circulating estradiol levels. Kalra and Kalra (1974) reported that the administration of progesterone on diestrous I blocked the expected afternoon rise of systemic estradiol as well as ovulation. These authors discussed the possiblity that progesterone may be capable of reducing systemic estradiol levels by a direct action on ovarian steroidogenesis in the rat.

The same has been postulated by Hess and Resko (1973) who observed that administration of progesterone in the intermenstrual period of the rhesus monkey reduced estradiol levels in serum.

The results presented here (Fig. 3) and reported in the literature on the ability of progesterone to reduce estradiol levels in serum possibly by means of a direct effect on ovarian steroidogenesis may serve as a further support of the hypothesis of Hoffmann (1962) who presented experimental evidence for the concept that progesterone may have a suppressive effect on the follicles of the corpus luteum bearing ovary and may thus favor indirectly the growth of the follicles of the contralateral ovary and alternating ovulation in the human female.

17-OHP has been claimed to be additionally involved in the regulation of the LH discharge at midcycle because of the characteristic change of its serum concentration during the periovulatory phase (Vande Wiele et al., 1970; Abraham et al., 1972). Our own studies demonstrate that 17-OHP was ineffective in inducing an LH and FSH surge in the midfollicular phase of the cycle with and without pretreatment with ethinyl-estradiol. These results correspond with observations made in the estrogen pretreated castrated female rat (Swerdloff et al., 1972).

20-DHP is regarded to play an important role in the regulation of the LH discharge and ovulation in the rodent. It prolongs the preovulatory LH discharge in the rabbit (Hilliard et al., 1967) and can induce an LH and FSH surge in the estrogen pretreated castrated female rat (Swerdloff et al., 1972). The results presented here indicate that 20-DHP is able to induce a positive feedback effect on LH serum concentrations in an estrogen primed eugonadal woman (Fig. 13). With respect to the slow increment in serum concentrations of 20-DHP during the periovulatory phase of the human menstrual cycle (Wu et al., 1974; Leyendecker et al.,

1975b) it seems to be very questionable that 20-DHP plays a genuine role in the regulation of the LH miccycle peak. However, as being principally effective it might – together with progesterone – constitute a part of the effective gestagen concentration.

Acknowledgment. The skilful technical assistance of Miss R. Klasen, Miss B. Leffek and Mr. E. Jost is gratefully acknowledged.

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Received January 8, 1976