

Induction of Ovulation with Chronic Intermittent (Pulsatile) Administration of LH-RH in Women with Hypothalamic and Hyperprolactinemic Amenorrhea*

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Ovulationsauslösung durch pulsatorische LH-RH-Gabe bei Patientinnen mit hypothalamischer und hyperprolactinämischer Amenorrhoe

Zusammenfassung. Fünf Frauen mit hypothalamischer Amenorrhoe wurden mit LH-RH behandelt (10–15 μg i.v. im Abstand von 90 min über 14–20 Tage). Bei allen Frauen führte diese chronisch-intermittierende LH-RH-Gabe zu einer Normalisierung der Gonadotropinspiegel im Serum. Bei vier Frauen kam es zu präovulatorischen Östradiolspiegeln mit nachfolgenden LH-Gipfeln im Serum. Bei drei Frauen führten die LH-Maxima zu Ovulationen, wie aus den Progesteronwerten im Serum zu schließen war. Bei einer weiteren Patientin mit einer hyperprolactinämischen Amenorrhoe führte die gleiche Therapie ebenfalls zur Ovulation. Diese Ergebnisse weisen darauf hin, daß bei Patientinnen mit hypothalamischer Amenorrhoe durch chronische Gabe von LH-RH eine normale hypophysär-ovarielle Funktion wiederhergestellt werden kann; sie lassen des weiteren die Vermutung zu, daß bei der Frau – wie bei der Rhesusäffin – die hypothalamische LH-RH-Funktion lediglich einen permissiven Charakter hat und die zyklische Regulation während des menstruellen Zyklus auf den Ebenen von Hypophyse und Ovar erfolgt. Die Amenorrhoe bei einer Hyperprolactinämie wird offenbar durch eine eingeschränkte hypothalamische Sekretion von LH-RH verursacht, wie die erfolgreiche Substitution durch chronisch-intermittierende LH-RH-Gabe zeigt. Erhöhte Prolaktinspiegel per se interferieren offenbar weder mit dem hypophysären positiven Feedback-Mechanismus noch mit der Gonadotropinwirkung auf ovarieller Ebene.

Schlüsselwörter: Hypothalamische und hyperprolactinämische Amenorrhoe – Auslösung der Ovulation – LH-RH

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Summary. Five women with hypothalamic amenorrhea were treated with LH-RH (10–15 µg i.v. at 90 min intervals for 17–20 days). In all women this chronic intermittent LH-RH administration resulted in a normalization of serum gonadotropin levels. Four women exhibited preovulatory estradiol serum levels with subsequent LH peaks. In three women the LH peaks were followed by normal luteal phase serum progesterone levels. One woman with hyperprolactinemic amenorrhea was also treated with the same therapeutic regimen which induced ovulation as judged from normal luteal phase serum progesterone levels. The results indicate that normal pituitary-ovarian function can be established in hypothalamic amenorrhea by chronic intermittent administration of LH-RH. They also suggest that in the human female hypothalamic LH-RH function may be only permissive in that the cyclicity of endocrine events during the menstrual cycle is regulated on pituitary and ovarian levels. Hyperprolactinemic amenorrhea appears to be associated with insufficient endogenous LH-RH secretion which can be substituted by exogenous chronic intermittent administration of LH-RH. Elevated prolactin levels per se do not interfere with the pituitary positive feedback mechanisms nor with the gonadotropin action on the ovarian level.

Key words: Hypothalamic and hyperprolactinemic amenorrhea — Induction of ovulation — Luteinizing hormone-releasing hormone (LH-RH) — Pulsatile substitution

In the ovariectomized, hypothalamus lesioned rhesus monkey with abolished pituitary gonadotropin release the intermittent administration of LH-RH re-established gonadotropin secretion. Additional administration of estradiol induced negative and positive feedbacks on pituitary gonadotropin release indicating that negative and positive feedback mechanisms of ovarian steroids are probably localized on the pituitary level in the primate (Nakai et al. 1978).

There is indirect evidence that hypothalamic ovarian failure in the human female is associated with reduced or deficient hypothalamic LH-RH secretion (Leyendecker 1979). Thus, this type of endocrine dysfunction may serve as a model to study in the human (a) whether pituitary and ovarian function can be normalized by circhoral intermittent administration of LH-RH, (b) whether hypothalamic LH-RH function is only permissive in character with ovarian steroid feedback mechanisms being localized on the pituitary level, and (c) whether chronic intermittent administration of LH-RH can be used as a therapeutic regimen in hypothalamic ovarian failure.

Material and Methods

Five women with normoprolactinemic hypothalamic and one woman with hyperprolactinemic amenorrhea volunteered for this study. All patients were "progestogen and clomiphene negative" (Leyendecker, 1979). A chronic antecubital venous catheter was used for the administration of LH-RH and for the drawing of the blood samples. On the day prior to the begin of chronic intermittent LH-RH administration a 100 µg i.v. bolus of LH-RH was given for acute evaluation of pituitary gonadotropin function. LH-RH in doses of 10–15 µg was administered every 90 min over a period of 2–3 weeks. Blood samples were drawn twice daily at 9 a.m. and 6 p.m. just before the next LH-RH bolus. On two days during treatment additional blood was drawn at 20 min intervals over a period of 4 h.

Serum LH and FSH concentrations were measured by radioimmunoassay (Thomas and Ferin 1968; Leyendecker et al. 1971), serum prolactin concentrations by the use of a commercially available radioimmunoassay kit (IDW, Dreieich, Frankfurt). Estradiol-17 β and progesterone in serum were determined by radioimmunoassay (Leyendecker et al. 1972, 1976).

Results

Patient S. H. (Fig. 1)

Figure 1 shows the results obtained in a 25-year-old woman with primary hypothalamic amenorrhea. Levels of LH, FSH and estradiol before and after the 100 μ g test

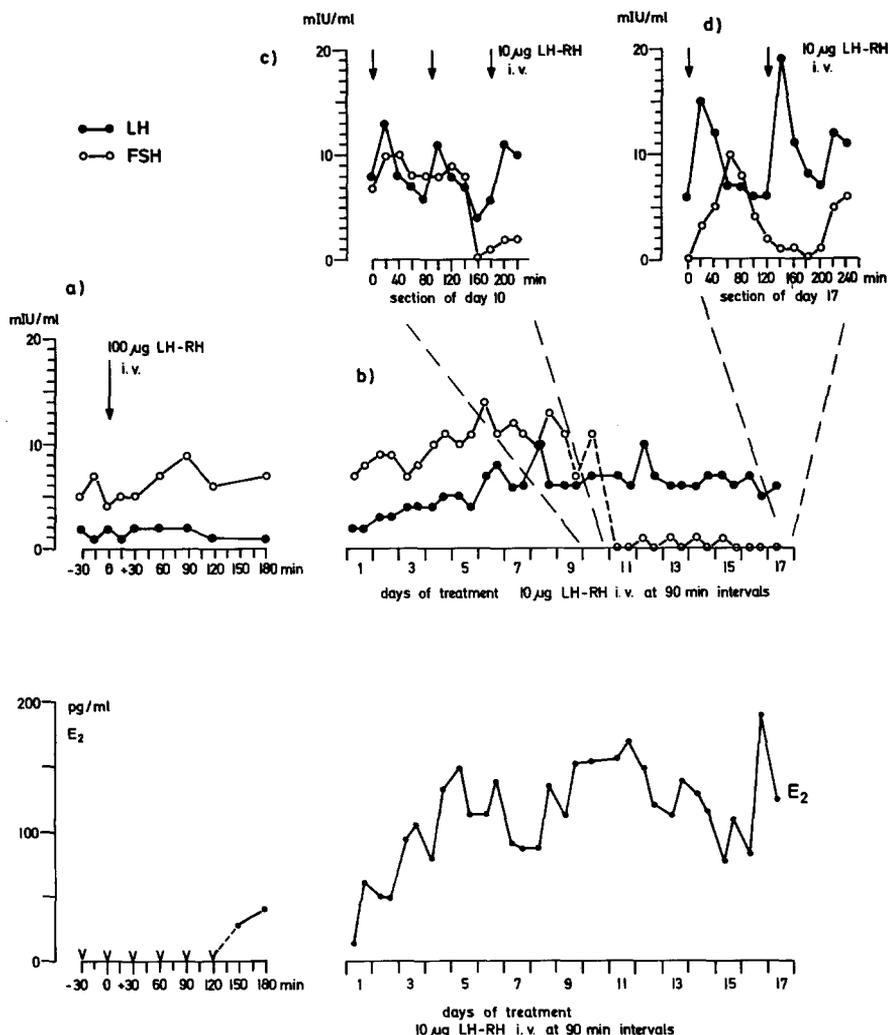


Fig. 1. FSH, LH, and estradiol serum levels in a 25-year-old woman (S. H.) with progestogen-negative primary amenorrhea. Following a LH-RH test with a test dose of 100 μ g of LH-RH i.v. the patient was treated with 10 μ g LH-RH i.v. every 90 min over a period of 17 days

dose of LH-RH (Fig. 1a) suggested dormant hypophyseal and ovarian functional. Shortly after the start of the chronic intermittent LH-RH administration the serum levels of LH-FSH and estradiol started to rise, the latter reaching values of the normal mid-follicular phase (Fig. 1b). Values obtained on days 10 and 17 (Fig. 1c and d) demonstrate that the pituitary gonadotropin levels now rose in response to only 10 μg of LH-RH having previously been unaffected by 100 μg of LH-RH.

Patient H. S. (Fig. 2)

Patient H. S. was a 22-year-old woman with primary hypothalamic amenorrhea in whom same regimen was used (Fig. 2). After a test dose of 100 μg of LH-RH a slight rise in gonadotropin levels was observed. During chronic intermittent treatment with 10 μg of LH-RH estradiol serum levels steadily increased indicating an improvement of pituitary and ovarian function. When preovulatory serum estradiol levels were reached an abrupt pituitary release of LH and to a lesser extent of FSH occurred similar to the normal midcycle peaks of LH and FSH. On day 19 (Fig. 2d) the pulsatile pattern of serum LH levels corresponded to the pattern normally seen towards the end of a mid-cycle peak.

Patient M. S. (Fig. 3)

Patient M. S. was the 24-year-old sister of patient H. S. and had the same history and a comparable severity of impairment of the hypothalamic-pituitary-ovarian axis as judged by the LH-RH test (Fig. 3). During intermittent administration of LH-RH the dose was raised to 15 μg per bolus. Serum estradiol levels steadily rose to the normal preovulatory range. Following an LH and FSH surge on days 14 and 15, progesterone levels began to rise rapidly indicating ovulation and corpus luteum formation.

Patient M. K. (Fig. 4)

In a 20-year-old woman with secondary hypothalamic amenorrhea the pituitary response to 100 μg of LH-RH revealed that the function of the hypothalamic-pituitary axis was impaired to a lesser extent as compared to the three patients presented above (Fig. 4a). Within 9 h after the begin of the chronic intermittent administration of LH-RH with 10 μg per bolus (Fig. 4b) estradiol levels in serum rose abruptly. This rise was followed by a further increase in serum estradiol and on days 6 and 7 LH and FSH peaks in serum occurred. The progesterone levels reached normal midluteal phase values subsequently indicating ovulation and subsequent corpus luteum formation.

Patient G. Q. (Fig. 5)

Patient G. Q. was a 31-year-old woman with secondary hypothalamic amenorrhea; the pituitary response to the test dose of 100 μg of LH-RH was similar to that of the patient (M. K.) (Fig. 5). After the onset of intermittent administration of 15 μg doses of LH-RH the basal gonadotropin levels rapidly increased. As in patient M. K. there was a concomitant abrupt rise of serum estradiol. Following a further steady rise

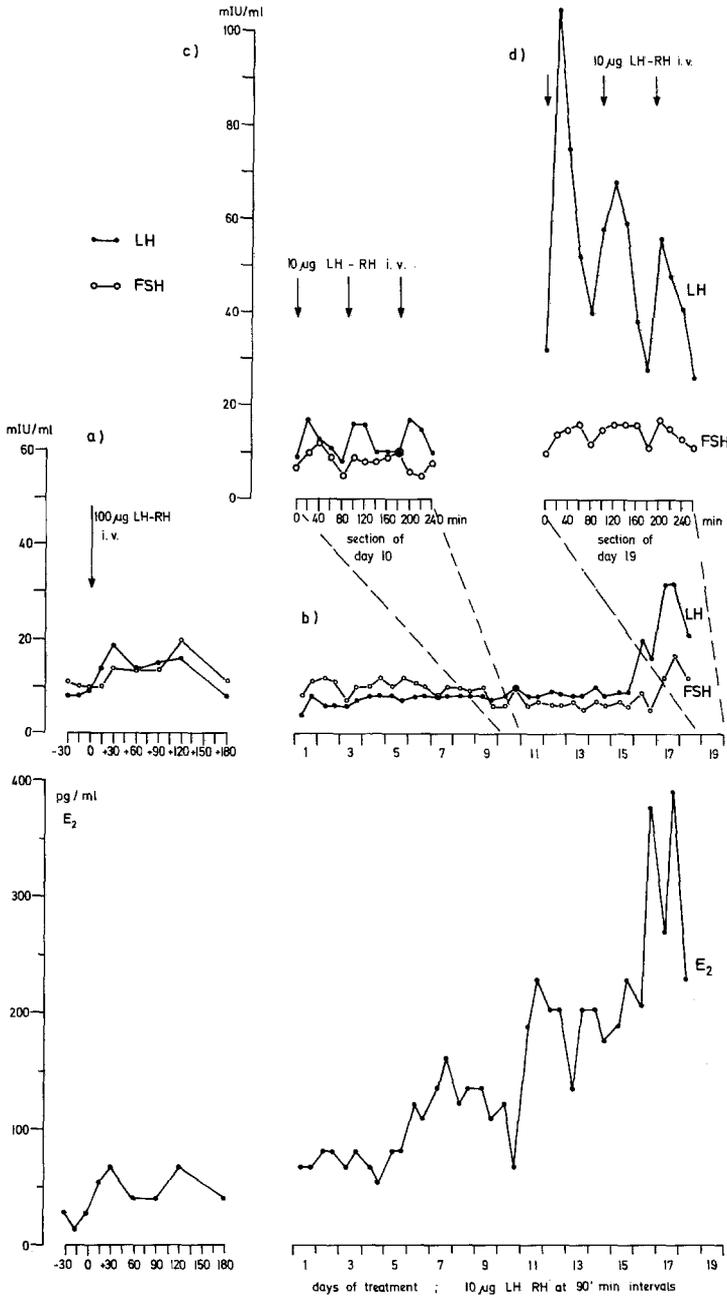


Fig. 2. FSH, LH, and estradiol levels in a 22-year-old woman (H. S.) with progesteron-negative primary amenorrhoea. Same treatment schedule as in Fig. 1

of serum estradiol abrupt pituitary releases of LH and FSH occurred. Corpus luteum formation was indicated by a rapid rise of progesterone during the following days. An artificial insemination was performed on the day of presumed ovulation (day 7 of

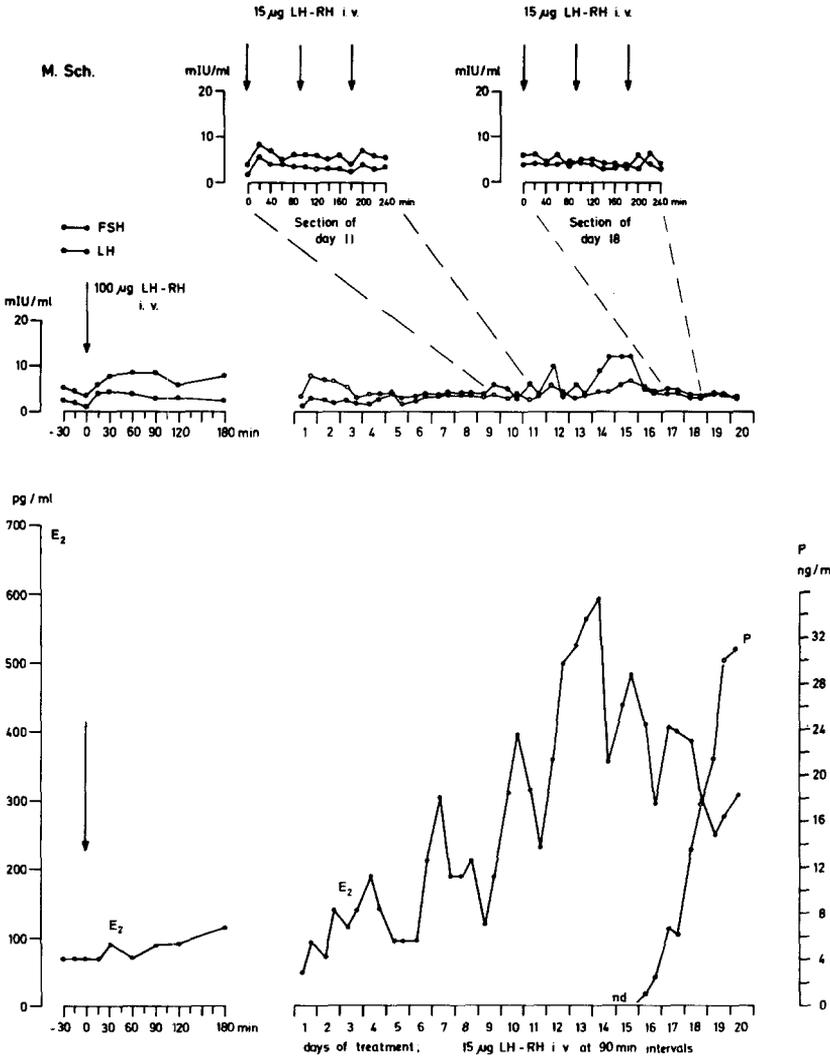


Fig. 3. FSH, LH, estradiol, and progesterone serum levels in a 24-year-old woman (M.S.) with progestogen-negative primary amenorrhea. Following a LH-RH test chronic intermittent LH-RH administration was performed over a period of 20 days with 15 µg LH-RH i.v. per bolus

treatment). A single i.m. dose of 10,000 IU of HCG was administered on day 13 of LH-RH treatment and intermittent LH-RH administration was discontinued. The patient did not conceive during this course of treatment.

Patient B. H. (Fig. 6)

B. H. was an 18-year-old patient with secondary hyperprolactinemic amenorrhea and basal serum prolactin levels in the range of 150 ng/ml; she had no evidence of pituitary adenoma (Fig. 6). The response to the LH-RH test was comparable with those

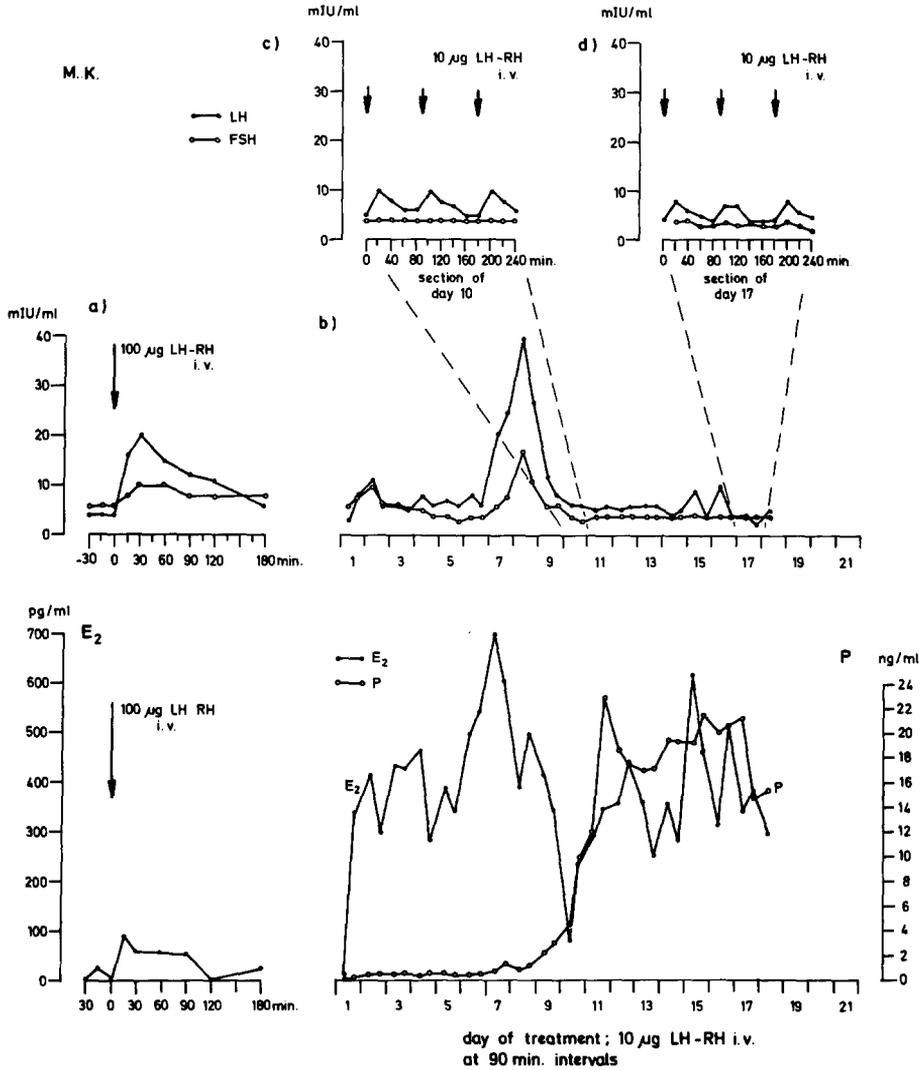


Fig. 4. FSH, LH, estradiol, and progesterone serum levels in a 20-year-old woman (M.K.) with progestogen-negative secondary amenorrhea. Same treatment as in Fig. 1

obtained in the normoprolactinemic patients M. K. and G. Q. Soon after treatment with intermittent LH-RH (10 µg per bolus) was started, serum gonadotropin levels became normal and there was a rapid increase in serum estradiol levels. Following serum LH and FSH peaks serum progesterone reached normal luteal phase levels within 8 days of assumed ovulation. With the termination of LH-RH administration at 9 a.m. on day 19 a rapid decline of serum LH to pretreatment levels occurred. At the same time the serum progesterone concentration began to fall indicating a cessation of corpus luteum function. The serum prolactin levels, which had gradually risen during treatment, also returned to the pretreatment values within a few hours.

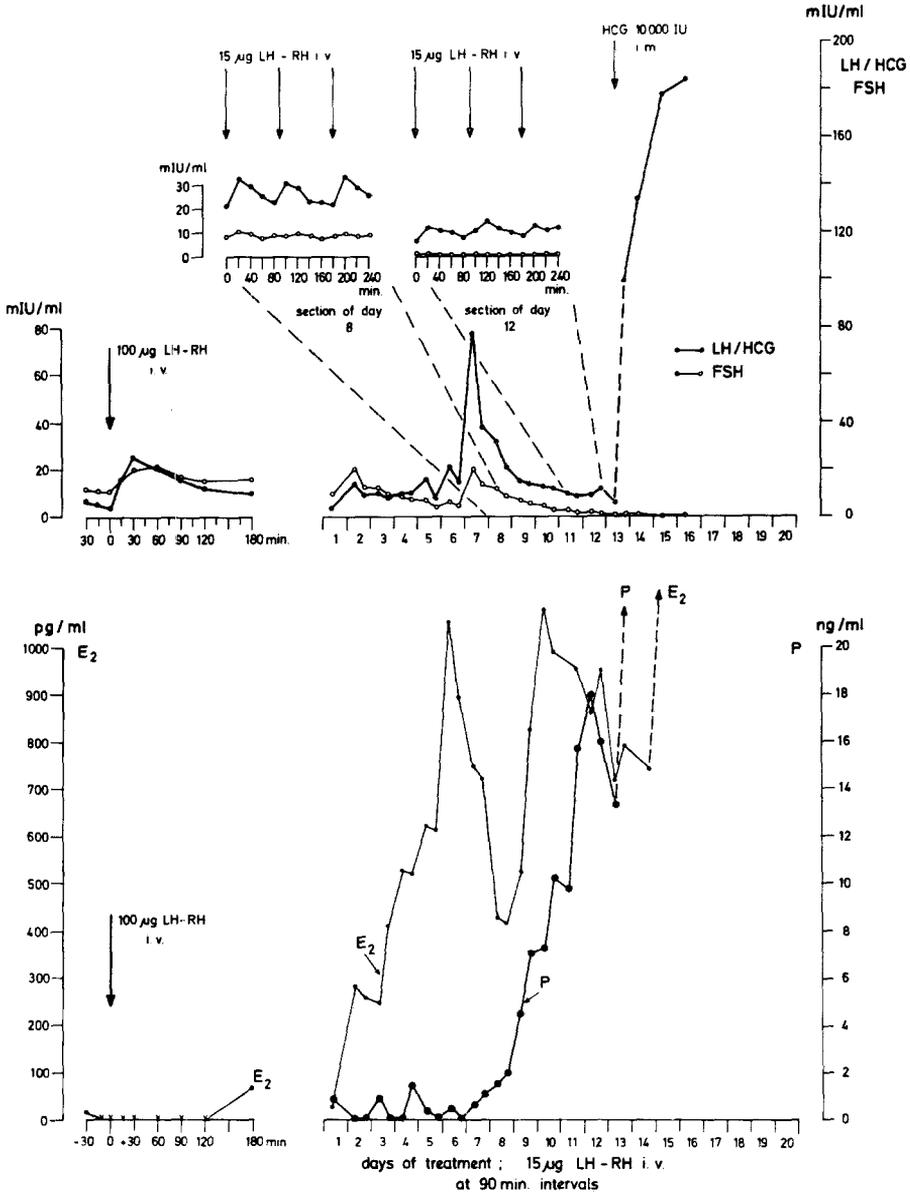


Fig. 5. FSH, LH, estradiol, and progesterone serum levels in a 31-year-old woman (G.Q.) with progestogen-negative secondary amenorrhea. Same treatment schedule as in Fig. 1. On day 13 of the treatment the patient received a single i.m. injection of 10,000 IU of HCG to further support the function of the corpus luteum. The increasing 'HCG' levels were estimated with the radioimmunoassay for LH

Discussion

There is indirect evidence that hypothalamic ovarian failure is associated with a reduced and deficient hypothalamic LH-RH secretion (Leyendecker 1979). This thesis

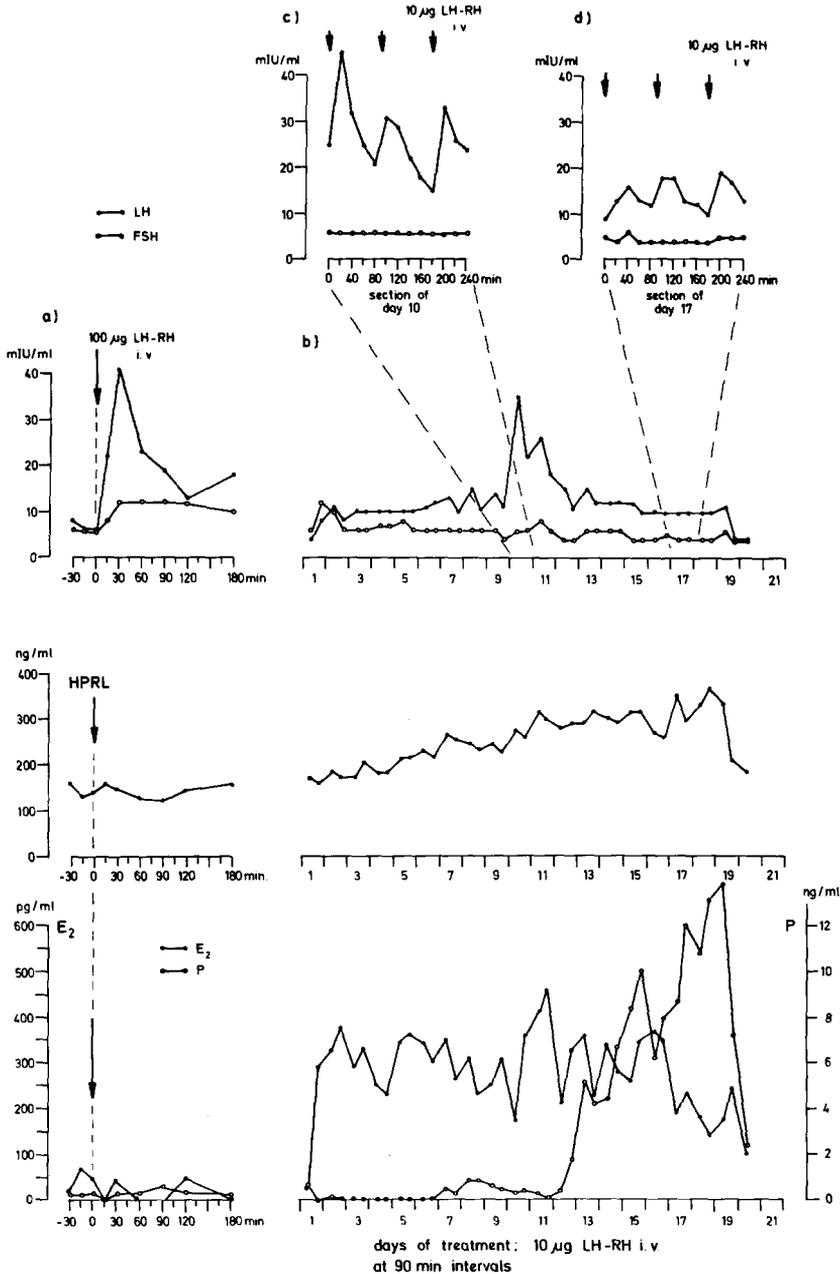


Fig. 6. FSH, LH, prolactin, estradiol, and progesterone serum levels in an 18-year-old patient (B. H.) with secondary hyperprolactinemic amenorrhea. Same treatment schedule as in Fig. 1

is indirectly supported by the results of this study. They demonstrate that presumably deficient endogenous LH-RH can be readily substituted by exogenous administration resulting in normalized pituitary and ovarian function.

In all the patients studied basal gonadotropin serum levels normalized following the institution of the chronic intermittent administration of LH-RH. The patterns of LH and FSH serum concentrations during the artificial cycles did not differ from those observed in normal menstrual cycles (Figs. 2–5). Similar to the pattern during a physiological proliferative phase (Ross et al. 1970; Leyendecker et al. 1975) initially elevated serum FSH levels gradually decreased towards ‘midcycle’, probably as a result of increasing ovarian negative feedback inhibition of pituitary FSH. Also similar to the normal proliferative phase LH levels remained unchanged or even slightly rose prior to the midcycle surges (Figs. 2–5).

Also, the ‘midcycle peaks’ of LH and FSH induced during the chronic intermittent administration of LH-RH did not differ from those of the normal menstrual cycle. The pulsatile pattern of serum LH during the proliferative phases and the descending limb of one midcycle (Fig. 2d) was similar to that observed during normal cycles (Yen et al. 1972).

Of special interest are the patterns of LH and FSH serum concentrations during the treatment in patient S. H. (Fig. 1). After a gradual increase of both LH and FSH serum levels a sudden drop of FSH levels occurred on day 10 of the treatment, while the LH serum levels remained unchanged. The decrease of only serum FSH is interpreted as the result of a selective ovarian negative feedback inhibition of pituitary FSH and is functionally comparable to the gradual decrease of serum FSH during follicular maturation in the other patients and during the late follicular phase of the normal menstrual cycle. In patient S. H. with presumably absent endogenous LH-RH secretion the exogenous administration of LH-RH in doses of 10 μg per bolus was not sufficient to maintain the initially normalized pituitary FSH function in the presence of an increasing ovarian negative feedback inhibition. However, in the other patients with a presumed presence of some endogenous LH-RH secretion, the additional exogenous LH-RH administered was sufficient to oppose the increasing ovarian inhibitory effects on pituitary FSH function, thus maintaining serum FSH levels which allowed further promotion of follicular maturation.

The ovarian responses following the stimulation of the gonadotrophs with LH-RH differed among patients. While in patients S. H., H. S., M. Sch. (Figs. 1–3) the estradiol levels in serum rose gradually over a period of several days, there was an unphysiologically sharp increase in serum estradiol already during the first 9 and 24 h in patients M. K. and G. Q. (Figs. 4 and 5), respectively. Probably, in the latter patients (M. K.; G. Q.), who had a less impaired hypothalamic and thus gonadotropic and ovarian function than the other patients, a set of ovarian follicles had gained a certain degree of morphological and functional maturity which allowed a prompt increase of ovarian estradiol synthesis as soon as the gonadotropin levels had become normal.

A 90 min interval between the single i.v. injections was chosen on the basis of observations that during the normal proliferative phase of the cycle the pulsatile discharges of LH occur approximately every 90 min (Yen et al. 1972). The dose of 10–15 μg of LH-RH per bolus was chosen because it resulted in peripheral venous and thus consequently in pituitary blood levels (unpublished) which were in the range of LH-RH concentrations of human pituitary blood (Antunes et al. 1978). The induced pulsatile patterns of serum LH during intermittent administration of LH-RH is undistinguishable from the normal oscillatory pattern of serum LH during the follicular phase of the cycle. This observation also suggests that the injection of 10–15 μg of LH-RH re-

sulted in LH-RH concentrations on the pituitary level within the physiological range.

Pulsatile intermittent LH-RH stimulation of the pituitary appears to be a prerequisite for normal gonadotropic function since the continuous application of LH-RH in the hypothalamus lesioned rhesus monkey resulted in a break down of pituitary gonadotropic function (Belchetz et al. 1978). The requirement of a pulsatile stimulation of the pituitary gonadotrophs may also explain why the longterm application of long acting LH-RH analogues did not result in an improvement but rather a deterioration of pituitary gonadotropic function (Dericks-Tan et al. 1977; Hanker et al. in press).

Previous attempts to induce follicular maturation and ovulation in severe hypothalamic amenorrhea or anorexia nervosa using LH-RH were not successful (Breckwoldt et al. 1974; Gual and Lichtenberg 1976) or required up to 10 times higher doses when a therapeutic regimen with 2–3 applications of LH-RH per day was chosen (Nillius 1976). While in the study of Nillius et al. (1975) a daily dose of 1500 μg of LH-RH was used, a daily dose of only 160–240 μg of LH-RH was sufficient to induce ovulation in the severely amenorrhic patients of our own study.

New data on the function of the hypothalamic-pituitary axis may provide an explanation for this discrepancy. Each pulse of LH-RH not only induces the release but also the synthesis of gonadotropins, the latter being accomplished approximately one hour following the LH-RH stimulus. By LH-RH double stimulation tests it was demonstrated that the LH response to a second LH-RH bolus was optimal in the amount of LH released if the second bolus followed the first one with a lapse of 60–180 min. When shorter or longer intervals between the two injections were chosen the pituitary response to the second stimulus was less than that to the initial one (Römmler 1978).

These observations were further substantiated by ultrastructural studies of the rat pituitary gonadotrophs: Parallel to the LH-RH induced extrusion of LH secretory granules new secretory granules appeared 1–2 h following the administration of LH-RH (Römmler et al. 1978).

These findings indicate that the pituitary gonadotrophs are subjected to LH-RH induced circroral functional cycles, consisting of intimately correlated processes, such as release, synthesis, storage, and intracellular degradation of gonadotropins (Römmler et al. 1978). These processes may be further modulated by the pituitary effects of gonadal steroids. In addition, cyclicity of hypothalamic stimulation of the pituitary gland may result in a functional synchronization of all or at least a great proportion of the gonadotrophs, thus rendering the hypothalamic-gonadotrophic unit an economic system with respect to the amount of LH-RH required for adequate pituitary stimulation.

In view of these considerations and findings the circroral pulsatile administration of LH-RH meets the functional requirements of the hypothalamic-pituitary unit. It is conceivable that with this regimen of therapy a much smaller total dose of LH-RH is required for the induction of ovulation than with other modes of LH-RH administration.

The results of our study indicate that in hypothalamic ovarian failure normal pituitary-ovarian function can be temporarily established by chronic intermittent administration of LH-RH. They suggest — since the dose of LH-RH per injection was not changed during the course of treatment — that also in the human female hy-

pothalamic LH-RH function may be only "permissive" (Knobil, pers. comm.) in that the cyclicity of endocrine events during the menstrual cycle is regulated only on pituitary and ovarian levels.

At the present time, however, direct proof cannot be provided which excludes an increase of endogenous hypothalamic LH-RH secretion being in part responsible for the gonadotropin surges during chronic intermittent LH-RH substitution. However, there is indirect evidence provided by our own study and that of others which excludes a substantial endogenous LH-RH contribution to the generation of the LH and FSH peaks.

In the normally cycling woman repetitive administration of 10 μg of LH-RH during different phases of the menstrual cycle resulted in LH and FSH serum levels which exceeded the normal values 6 to 10 times (Wang et al. 1976). Repetitive administration of 10 μg of LH-RH to estradiol- and progesterone-pretreated women during the early follicular phase of the menstrual cycle resulted in LH surges which exceeded the height of the normal LH midcycle peak 3 to 6 times (Lasley et al. 1975). In our own study of chronic intermittent LH-RH substitution in hypothalamic amenorrhea, however, the serum concentrations of LH and FSH never exceeded the physiological range. It is therefore unlikely that a substantial estradiol-induced increase in pituitary LH-RH concentration during "midcycle" had occurred being attributable to a positive feedback effect of estradiol on the hypothalamic level.

A solely permissive function of LH-RH in the regulation of the menstrual cycle would facilitate the clinical application of chronic intermittent administration of LH-RH in the treatment of hypothalamic ovarian failure, since during follicular maturation and prior to ovulation no readjustments in the dose of LH-RH are required. Work is in progress to evaluate the applicability of a miniaturized LH-RH dispenser in clinical practice (Leyendecker, in prep.).

Ovarian failure in hyperprolactinemia was suggested to be caused by an inhibitory effect of elevated prolactin concentrations directly on the ovarian level (McNatty et al. 1974). Pituitary and hypothalamic sites of interference of elevated levels of prolactin with reproductive function had also been taken into consideration (London et al. 1977; Van Look et al. 1977). In our own study chronic intermittent administration of LH-RH in a patient with hyperprolactinemic amenorrhea (Fig. 6) induced normal gonadotropic pituitary and ovarian function. Thus, indirect support was provided for the notion that in hyperprolactinemia ovarian failure may be associated with deficient endogenous LH-RH release. Elevated prolactin levels per se do not seem to interfere with the positive feedback action of ovarian steroids on pituitary gonadotropin release nor significantly with the gonadotropin action on the ovarian level, since the response of the pituitary-ovarian axis to the chronic intermittent administration of LH-RH was essentially the same in the hyperprolactinemic (Fig. 6) as in the normoprolactinemic patients (Figs. 4 and 5).

In all our patients a withdrawal bleeding occurred following the termination of the therapy, and the amenorrhic state was resumed subsequently. There were no indications that the temporary substitution therapy with LH-RH had permanently improved the impaired hypothalamic function in these women.

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