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The pathophysiology of hypothalamic ovarian failure *

Diagnostic and therapeutical considerations

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Intensive research in reproductive endocrinology over the past decade has resulted in a tremendous accumulation of knowledge concerning the physiology and pathology of the endocrine regulation of the human menstrual cycle. This review will be confined to secondary normoprolactinemic (hypothalamic) ovarian failure, with special emphasis being put on the elaboration of a concept of its pathophysiology. Based on this concept, diagnostic and therapeutic aspects will be discussed, including the substitution therapy with gonadotropin-releasing hormone.

Prior to presenting and reviewing some experimental data obtained in patients suffering from hypothalamic ovarian failure and which will serve for the elaboration of a concept of the pathophysiology of this condition, the regulation of the hypothalamic–pituitary–ovarian axis during normal follicular maturation will be briefly summarized.

The hypothalamic–pituitary–ovarian axis during normal follicular maturation

Figure 1 is a schematic representation of the endocrine changes during the proliferative phase of the human menstrual cycle. There is direct and indirect experimental evidence from studies in the rhesus monkey (Dierschke et al., 1970; Carmel et al., 1976) and indirect evidence from studies in the human female (Yen et al., 1972) that hypothalamic LH-RH is secreted into the portal circulation in a pulsatile fashion, with a frequency of one pulse every 60–120 min. Observations of an increased pituitary response towards identical LH-RH stimuli during the periovulatory phase as compared to earlier stages of the cycle (Lasley et al., 1975), as well as recent data from the hypothalamus-lesioned rhesus monkey (Knobil and Plant, 1978; Nakai et al., 1978), indicate that for the generation of the LH mid-cycle surge no further increase of hypothalamic LH-RH secretion is required.

An adequate LH-RH secretion provided, the pituitary synthesizes and secretes FSH and LH in an adequate amount, which in turn stimulates follicular maturation. With its secretory products, mainly estradiol and perhaps inhibin (H. Becker, personal communication), the growing follicle feeds back on FSH and LH secretion, thus controlling its own maturation process. This feedback probably takes place mainly on the level of the pituitary gonadotropes, and affects FSH and LH in a very different manner. While inhibiting synthesis as well as secretion of FSH, estradiol seems mainly only to inhibit pituitary secretion of LH, leaving synthesis of LH unaffected (Barraclough and Haller, 1970; Yen and

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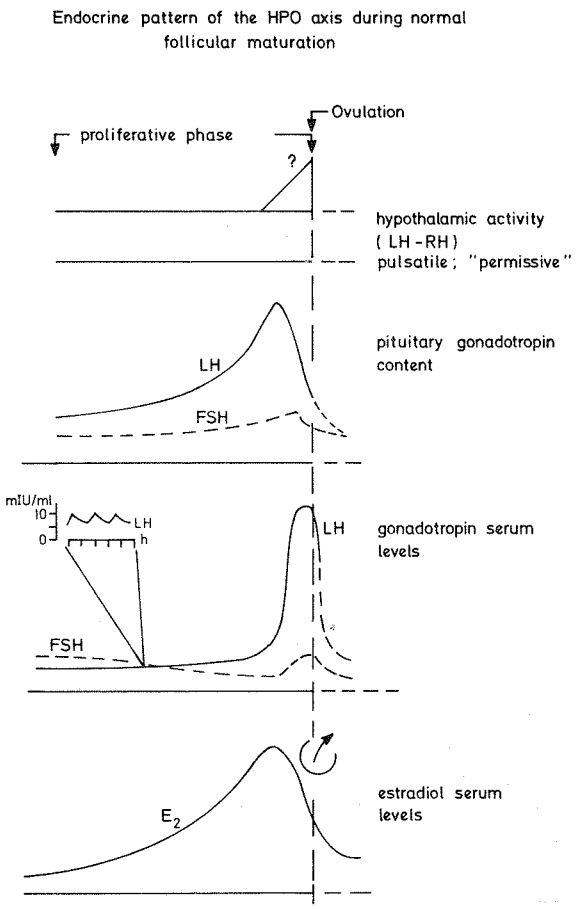

Fig. 1. Schematic representation of the endocrine pattern of the hypothalamic–pituitary–ovarian axis during the proliferative phase of the human menstrual cycle. (Modified from Leyendecker and Nocke, 1976.)

Tsai, 1971). The result is that, parallel to the maturation process of the follicle, the pituitary stores are increasingly filled with LH, and to a lesser extent with FSH (Leyendecker and Nocke, 1976). An estradiol-controlled dynamic balance seems to exist between pituitary LH storage and release, in that during the process of storage the amount of LH released only increases very gradually, as indicated by the small increase of serum LH levels during the proliferative phase of the cycle (Ross et al., 1970).

This dynamic balance of LH storage and release is disrupted when rapidly rising estradiol levels are maintained above a critical threshold for a certain duration of time (Knobil, 1974). Since no further LH-RH stimulation is required for the initiation of the LH surge, the mechanisms responsible for the functional change of the gonadotropes from storage to release mainly reside within the pituitary itself (Nakai et al., 1978). As a consequence of the functional change of the gonadotropes, of which the mechanism on the cellular level is as yet unclear, the pituitary stores are partially depleted and a precipitous rise of LH and, to a lesser extent, of FSH in serum will occur, initiating the process of ovulation.

On the ovarian level the maturational process is accompanied by the successive appearance of receptor sites for FSH, estradiol, testosterone, LH, prolactin and prostaglandins (Richards et al., 1976; Schreiber and Ross, 1976; Erickson, 1978). The early appearance of FSH receptors underlines the primary importance of this hormone for follicular development and function (Jones et al., 1969; McNatty and Sawers, 1975), and it can be demonstrated that in some forms of hypothalamic ovarian failure it is primarily the defective secretion of FSH which results in impaired ovarian function (vide infra).

The hypothalamic–pituitary–ovarian axis in hypothalamic ovarian failure

The CNS has long been recognized as a primary site of functional disturbances leading to ovarian failure. Thus, terms like psychogenic, stress or situational amenorrhea have been introduced to characterize these conditions. Even in less overt situations, careful psychological analysis revealed correlations between personality structures and the occurrence of amenorrhea (Reifenstein, 1946; Tietze, 1948; Fries and Nillius, 1973; Frick, 1974). Whatever the primary cause (i.e. stress or a certain disposition) and the neural links may be, the reduction or disappearance of the pulsatile fluctuation of LH serum levels in amenorrhea without evidence of impaired pituitary function strongly suggests that the pituitary–ovarian axis is finally affected by a reduction of hypothalamic LH-RH secretion. History and observation of such patients often reveals that corpus luteum insufficiency (CLI), anovulatory cycles, oligomenorrhea are transitory stages during development of or recovery from amenorrhea. It is therefore suggested that, in

secondary (hypothalamic) ovarian failure, CLI, anovulatory cycle, oligomenorrhea and amenorrhea form a pathophysiological entity on the basis of a gradually reduced hypothalamic LH-RH release.

Corpus luteum insufficiency

Figure 2 demonstrates the serum concentrations of LH, FSH, estradiol and progesterone in 4 women suffering from CLI as compared to the respective hormonal levels during the normal menstrual cycle. Clinically, CLI is characterized by inadequate increase

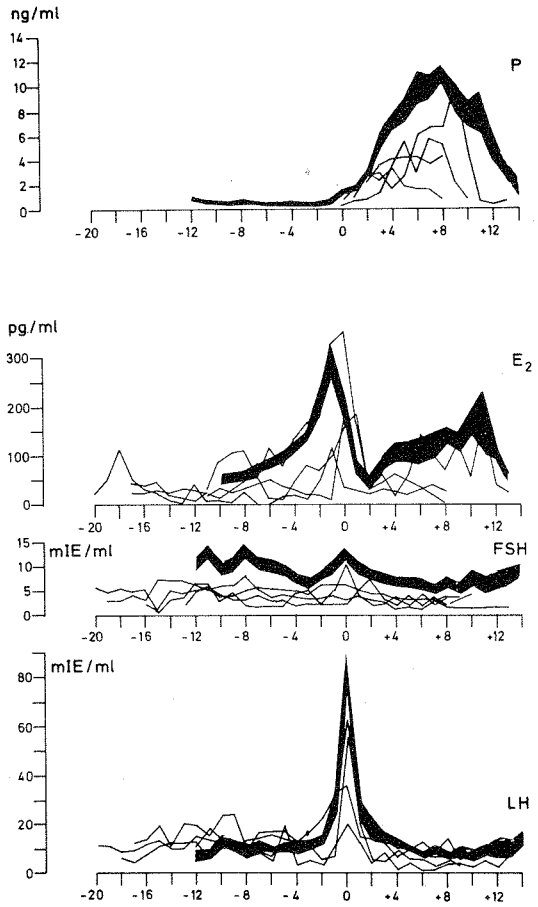

Fig. 2. FSH, LH, estradiol and progresterone serum levels during cycles with corpus luteum insufficiency in comparison to the respective hormone levels during the normal menstrual cycle (shaded area = mean ± SEM (n = 8). (Modified from Leyendecker et al., 1975.)

of BBT and/or duration of hyperthemia in the presence of short, normal or sometimes prolonged cycle length. Endocrinologically, subnormal levels of progesterone, resulting in inadequate hyperthermia, and of estradiol during the luteal phase are found (Strott et al., 1970; Sherman and Korenman, 1974; Leyendecker et al., 1975; Wilks et al., 1976).

Analysis of gonadotropin levels in serum reveals that in the presence of normal proliferative phase levels of LH the serum concentrations of FSH are in the subnormal range as compared to normal cycles (Strott et al., 1970; Sherman and Korenman, 1974; Leyendecker et al., 1975). While in the short luteal phase cycles of the rhesus monkey LH values are in the subnormal range throughout the whole cycle (Wilks et al., 1976), in CLI of the human female there is a trend of lower LH values mainly during the mid-cycle surge and during the luteal phase of the cycle (Strott et al., 1970; Leyendecker et al., 1975).

Strott et al. (1970) suggested that CLI is the result of inadequate FSH stimulation of the growing follicle. It can be derived from the normal ovarian pituitary interplay that insufficient follicular FSH stimulation must result in endocrine sequelae already visible during the proliferative and periovulatory phases of the cycle. Estradiol serum levels are often below normal and, since estradiol serum levels regulate the amount of LH stored, an insufficient amount of LH might be released to induce ovulation of a follicle, which itself might at the same time have an insufficient equipment of receptor sites. Dhont et al. (1974) could demonstrate that, in the normal cycle, by proper timing of estrogen administration the mid-cycle LH release and subsequent corpus luteum function could be augmented, indicating the role of preovulatory estradiol levels in the determination of the amount of LH released. Thus, insufficient FSH stimulation of the growing follicle might, at the time of ovulation, result in functional immaturity on the follicular as well as on the pituitary levels, leading to the formation of an insufficient corpus luteum.

Amenorrhea

Figure 3 demonstrates LH-RH infusion studies performed in 18 normoprolactinemic women suffering from amenorrhea. Women with anorexia ner-

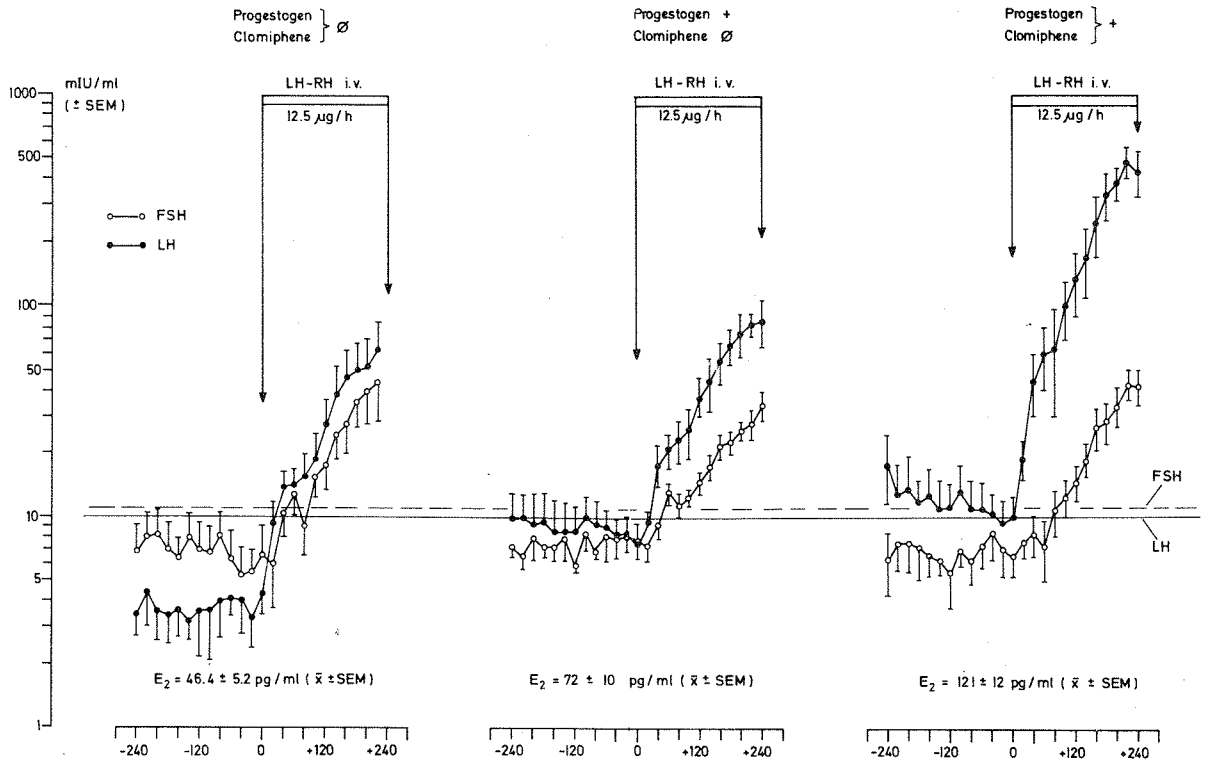

Fig. 3. FSH and LH serum levels during a 4 h period prior to and during a 4 h period of i.v. LH-RH infusion (12.5 µg/h) in 18 women with hypothalamic amenorrhea. The patients were divided into 3 groups according to the progestogen and clomiphene test results. Progestogen- and clomiphene-negative: n = 6; progestogen-positive/clomiphene-negative: n = 5; progestogen- and clomiphene-positive: n = 7. E_2 = basal estradiol serum levels. The dotted and the solid horizontal lines represent the mean serum levels of FSH and LH, respectively, of the normal proliferative phase.

vosa, anorectic reaction and with polycystic ovary syndrome were excluded. LH-RH was infused at a rate of 12.5 µg/h over a period of 4 h. During a 5 h preinfusion as well as during the infusion period, blood samples were drawn at 20 min intervals. The women were divided into 3 groups according to the results of the progestogen- (10 mg medroxyprogesterone acetate daily X10 days) and clomiphene- (100 mg of clomiphene acetate daily X5 days) tests, respectively. A test result was considered as positive when a vaginal bleeding followed the medication after an appropriate lapse of time.

Characteristic of all 3 groups of amenorrhea were the subnormal basal serum levels of FSH. Basal LH serum levels were extremely low in the progestogen- and clomiphene-negative group and had risen to slightly subnormal levels in the progestogen-positive but clomiphene-negative group. In the clomiphene-positive group basal LH serum levels were slightly above the normal proliferative phase mean.

As reflected from the gonadotropin increment in serum during LH-RH infusion, the mean pituitary FSH reserve did not differ among the 3 groups. Mean pituitary LH reserve was slightly larger in the second as compared to the first group, and was in the range of normal preovulatory values (unpublished data) in the third group. There was a positive correlation between the mean basal LH and estradiol serum levels as well as the result of the progestogen and clomiphene tests in the 3 groups.

Pathophysiological concept of the hypothalamic–pituitary–ovarian axis in hypothalamic ovarian failure

It has not yet been possible to measure endogenous LH-RH in the peripheral circulation in order to substantiate the notion of hypothalamic ovarian failure as the result of a reduced hypothalamic LH-RH release. Thus, this view is still only based on circumstantial evidence. We will attempt to demonstrate that the hormonal findings in secondary ovarian failure are compatible with this view, and that the various forms of hypothalamic ovarian failure constitute a pathophysiological entity.

Figure 4 is a schematic representation of this

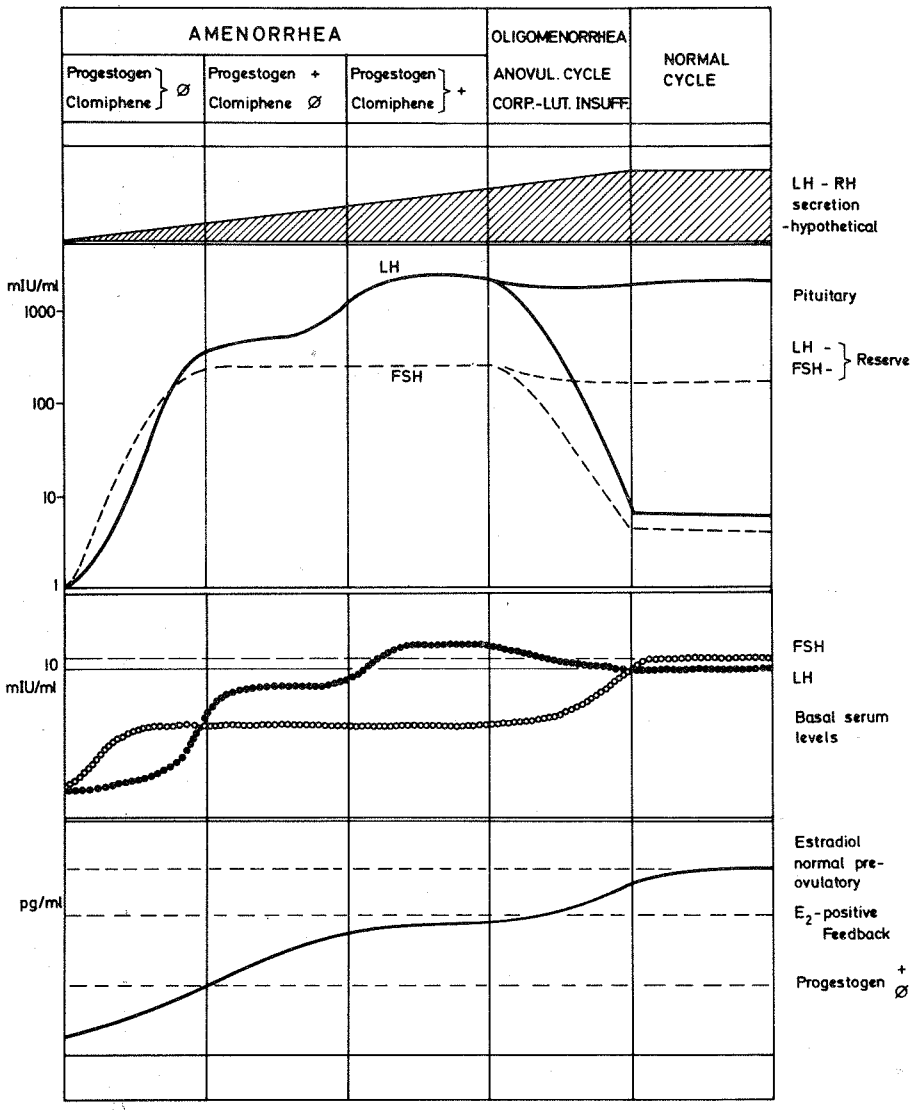

Fig. 4. A schematic representation of the pathophysiology of hypothalamic ovarian failure. Corpus luteum insufficiency, anovulatory cycles, oligomenorrhea and amenorrhea are believed to form a pathophysiological entity on the basis of a gradual reduction of hypothalamic LH-RH secretion. The pituitary gonadotropin reserve is depicted on the basis of a cumulative net increase of serum gonadotropin levels during LH-RH infusion. The separating lines for LH and FSH pituitary reserve indicate cyclically occurring changes of the pituitary reserve due to gonadotropin discharges.

concept. The normal menstrual cycle is characterized by an adequate and permissive hypothalamic secretion of LH-RH, resulting in an adequate secretion of FSH and LH from the pituitary gland. This in turn stimulates follicular growth, resulting in full follicular maturation, which is indicated by preovulatory levels of estradiol in serum. Serum estradiol feeds back on the pituitary gonadotropes, resulting in functional changes of the gonadotropes from accumulation of the gonadotropins to their acute release. This is illustrated in Figure 4 by the dividing lines for pituitary reserve.

Secondary ovarian failure is now interpreted as the result of a reduction or defect of hypothalamic LH-RH secretion. The changing ratios of FSH/LH basal serum levels in secondary ovarian failure are explainable when it is taken into consideration that ovarian negative feedback on gonadotropin secretion does not only take place during the normal menstrual cycle but is also operative in secondary ovarian failure and affects FSH and LH in a differential manner, with FSH being more subjected to ovarian negative feedback inhibition than LH.

In severe hypothalamic LH-RH deficiency there is only little or no stimulation of the pituitary gonadotropes and thus only little follicular stimulation. Due to the low estradiol serum levels the endometrium is not sufficiently proliferated to allow a secretory transformation following progesterone administration. As a result, the progestogen test is negative. Pituitary gonadotropin reserve is absent or low. FSH serum levels exceed those of LH, which are extremely low. The pituitary gonadotropes under this condition may be compared with perifused but unstimulated hemipituitaries, where FSH secretion also exceeds that of LH (Dowd et al., 1975).

In less severe cases of reduced hypothalamic LH-RH release (progestogen-positive/clomiphene-negative as well as clomiphene-positive forms of amenorrhea) the pituitary gonadotropes are stimulated, which is indicated by the rise of basal LH levels in serum. Concomitantly, estradiol serum levels increase, and perhaps together with inhibin selectively inhibit pituitary FSH. Thus, FSH levels remain low and a change in the FSH/LH ratio occurs.

A certain degree of follicular stimulation leads to proliferated endometrium, which can be transformed and shed by administration and withdrawal of progesterone, respectively. The progestogen test becomes positive. The clomiphene test remains negative as long as the neutralization of the ovarian negative feedback on the pituitary gonadotropes by the antiestrogen is not sufficiently supported by endogenous LH-RH secretion.

The clomiphene test becomes positive when, due to a more adequate endogenous LH-RH secretion, the administration of the antiestrogenic compound results in sufficient pituitary gonadotropin release, which in turn promotes follicular maturation. However, this stimulatory impulse only results in full follicular maturation and ovulation when the endogenous LH-RH secretion is strong enough to further support the maturational process of the follicle. Thus, the clomiphene-positive test result may be subclassified according to the occurrence of a vaginal bleeding following either anovulation, corpus luteum insufficiency or normal corpus luteum function as judged from BBT and serum progesterone measurements, reflecting different degrees of hypothalamic impairment within the clomiphene-positive group.

In this group of amenorrhea, with normalized serum levels of LH, the subnormal levels of FSH in serum seem to constitute the limiting factor for follicular maturation, resulting in estradiol serum levels which remain below the positive feedback threshold.

Due to chronic anovulation the pituitary gonadotropin stores are increasingly filled with LH. In the clomiphene-positive form of amenorrhea the pituitary reserve can even reach normal preovulatory values. In these cases also basal serum levels of LH resemble those found in the normal cycle just prior to the onset of the LH surge, which are usually higher than the mean values of the whole proliferative phase (Ross et al., 1970).

With further normalization of hypothalamic LH-RH secretion also basal FSH levels increase, follicular maturation progresses, estradiol levels rise further, and follicular atresia may result in estradiol withdrawal bleedings. Incidentally, estradiol-induced pituitary LH discharges with subsequent ovulations may occur, resulting in the clinical pictures of anovulatory cycles and/or oligomenorrhea, respectively.

Within the group of secondary ovarian failure with more or less cyclically occurring bleedings, the CLI probably constitutes the form with the least impair-

ment of hypothalamic LH-RH release. Negative feedback inhibition of the ovary on the secretion of FSH has been nearly overcome by endogenous LH-RH secretion, and follicular maturation progresses to a stage which induces positive feedback mechanisms and the subsequent formation of an, as yet, still insufficient corpus luteum.

In spite of improved LH-RH secretion in this condition as compared to clomiphene-positive amenorrhea, the pituitary LH reserve prior to ovulation is lower in CLI than in clomiphene-positive amenorrhea. While in the latter the huge LH reserve has been built up during a period of chronic anovulation, in CLI factors like cyclic LH discharge in combination with still insufficient LH-RH release and subsequently still insufficient estradiol serum levels prior to ovulation do not permit the pituitary to accumulate LH up to the potential capacity of the gland.

Only in the normal menstrual cycle, on the basis of an adequate and 'permissive' (Knobil, personal communication) LH-RH secretion, all the conditions are appropriately met to allow full maturation synchronically and interdependently on both the ovarian and pituitary levels, resulting in ovulation and normal corpus luteum function.

Diagnostic considerations

Following exclusion of hyperprolactinemia by measurement of prolactin, and of primary ovarian failure by measurement of FSH serum levels, the severeness of hypothalamic amenorrhea can readily be determined by the application of the progestogen and clomiphene tests. As demonstrated in Figures 3 and 4, these two tests allow a subtle evaluation of the function of the hypothalamic–pituitary unit. The LH-RH tests as usually performed do not add additional information in clinical practice. However, since the progestogen-negative group is comprised of LH-RH-responsive (Fig. 3) as well as -unresponsive patients (Fig. 5), the LH-RH test would allow a subclassification in this respect. On the basis of a negative LH-RH test result, however, no conclusion can be drawn as to the primary site (pituitary vs. suprapituitary) of the lesion, since neither a primarily deficient nor a long-term unstimulated pituitary would respond to a single LH-RH stimulus. Only a long-term LH-RH stimulation could allow a differentiation in this respect (Figs. 5 and 6).

Administration of estrogen to amenorrheic women has been shown sometimes to result in an acute release of LH from the pituitary gland, and has therefore been suggested as a test of pituitary–hypothalamic function in amenorrhea (Czygan and Reich, 1973; Shaw et al., 1975). Shaw et al. (1975) could demonstrate this in a group of 10 amenorrheic women who exhibited an acute LH release following the administration of 1 mg of estradiol benzoate ovulated following treatment with clomiphene. None of the 5 remaining subjects showed any increase in serum gonadotropin levels in response to estradiol benzoate, and, none ovulated on clomiphene. Thus, the estrogen provocation test adds additional information to the clomiphene test if the evaluation of the latter is merely based on the occurrence of a vaginal bleeding. If, however, the positive clomiphene test result is subclassified according to the occurrence of an anovulatory cycle, a corpus luteum insufficiency or a normal ovulation following the administration of clomiphene, which can be readily assessed by BBT chart and/or measurement of progesterone in serum, the information gained by the estrogen provocation test is within the scope of information obtained by the clomiphene test.

Oligomenorrhea, anovulatory cycles and corpus luteum insufficiency are readily diagnosed by BBT chart and/or measurements of serum progesterone during the presumptive secretory phase. A hyperprolactinemia should be considered and excluded as a possible causative factor (Wyss et al., 1977).

Therapeutical aspects and prospects of LH-RH substitution

Although, as can be seen in Figure 4, no form of hypothalamic ovarian failure is *normo*-gonadotropic, in clinical practice substitution therapy with exogenous gonadotropins is usually restricted to the clomiphene-negative forms of amenorrhea. In the less severe forms of hypothalamic ovarian failure the therapeutic regimen usually consists in the mobilization of endogenous gonadotropins by the administration of antiestrogenic compounds which may be sup-

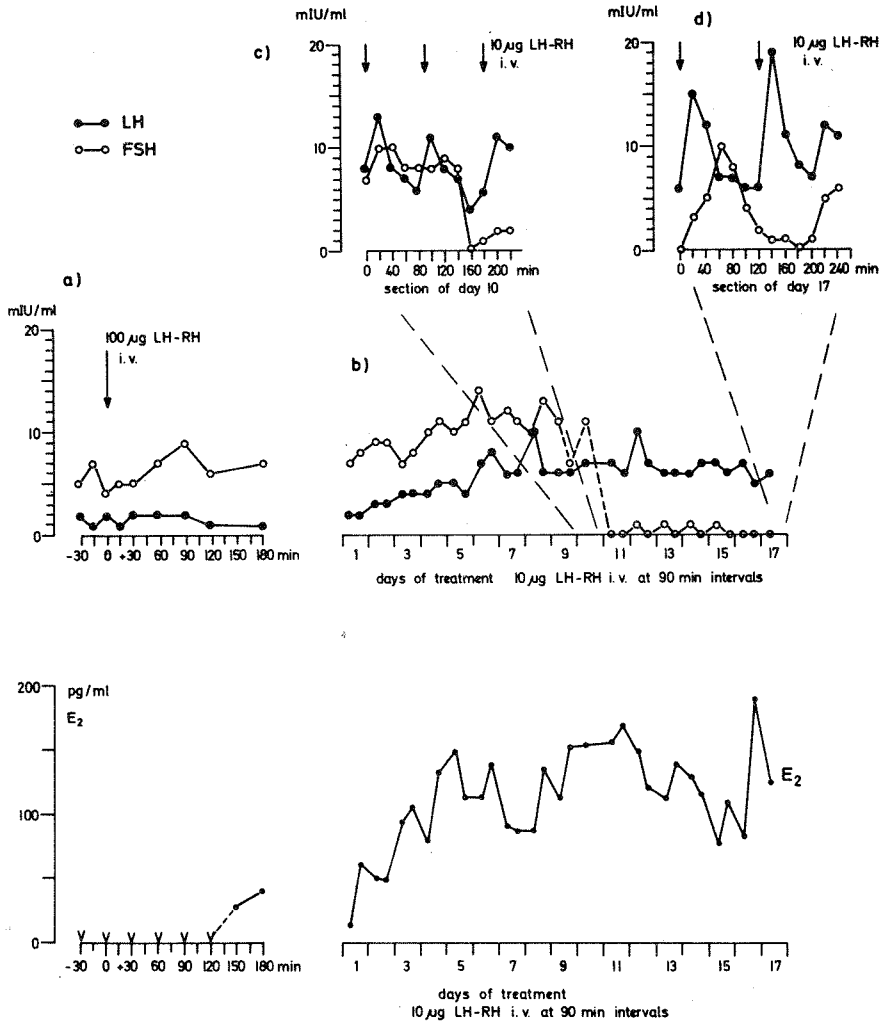

Fig. 5. FSH, LH and estradiol serum levels in a 25-yr-old woman with progestogen-negative primary amenorrhea. Following a LH-RH test with a test dose of 100 µg LH-RH i.v., the patient was treated with 10 µg LH-RH i.v. every 90 min over a period of 17 days.

ported by the properly timed additional administration of HCG, LH-RH and/or estrogen. It is evident from Figure 4 that, in forms where clomiphene is successful in inducing ovulation, it is the rise of FSH which is important, acting as the 'push' necessary for the initiation of development of a new set of follicles (Insler and Lunenfeld, 1976). The further maturational process is then carried on by the impaired function of the hypothalamic–pituitary unit, thus frequently resulting in luteal phase insufficiency (Van Hall and Mastoom, 1969).

In view of the hypothesis of normoprolactinemic secondary ovarian failure as the result of a deficient hypothalamic LH-RH secretion, it was predictable that LH-RH would be used therapeutically as soon as it was available in larger amounts. Some positive reports have been published and it was observed that, whenever ovulation or an ovarian response followed the administration of LH-RH, it was mainly restricted to the less severe forms of amenorrhea (Breckwoldt et al., 1974; Gual and Lichtenberg, 1976; Nillius, 1976). While Breckwoldt et al. could not observe any

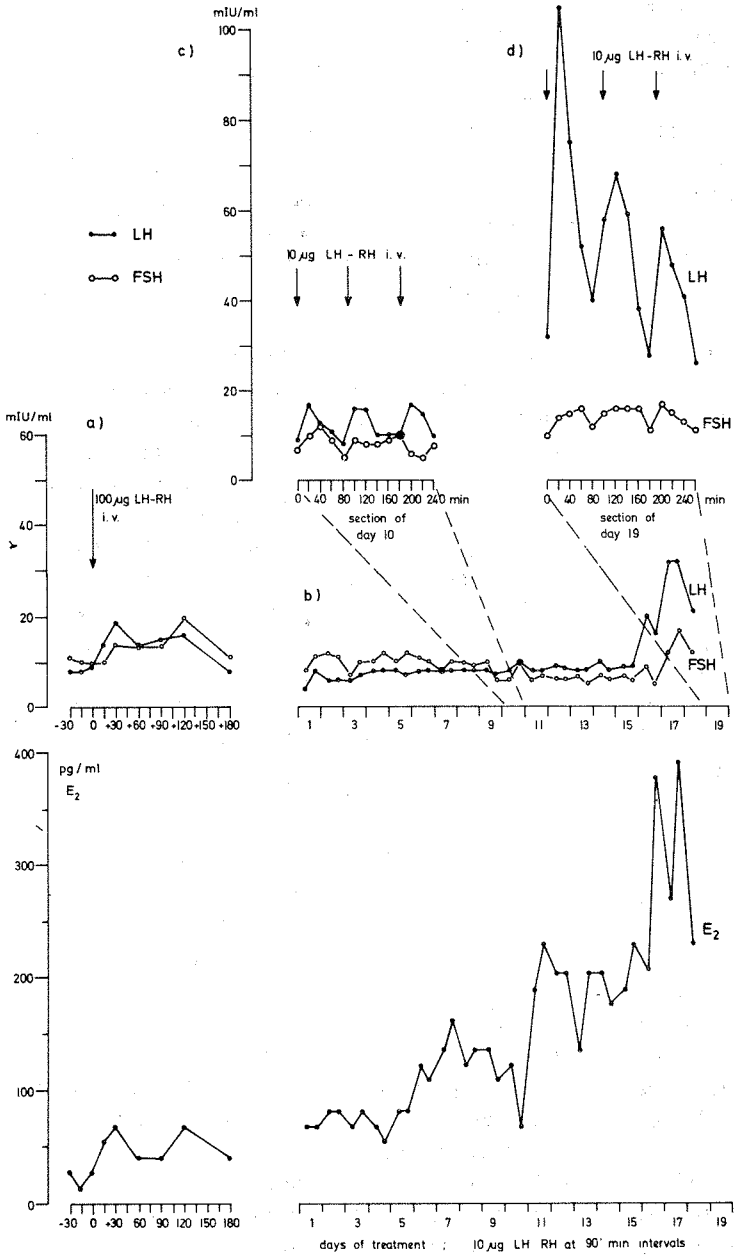

Fig. 6. FSH, LH and estradiol serum levels in a 22-yr-old woman with progestogen-negative secondary amenorrhea. Same treatment schedule as in Fig. 5.

ovarian response in 3 women with hypogonadotropic ovarian insufficiency during s.c. treatment with twice daily 100–200 µg of LH-RH over a period of 18–21 days, Nillius et al. (1975) could induce ovulations in 4 women suffering from anorexia nervosa by administration of 500 µg LH-RH 3 times per day over a period of 4 wk. However, as judged from progesterone serum levels, 3 of the 4 women exhibited luteal phase defects.

In view of the extreme subtlety of the regulation

of the HPO axis, it is conceivable that successes in the treatment of amenorrhea with exogenous LH-RH in a rather non-physiological mode had a more or less casual character.

Recent experimental data on the endocrine regulation of the hypothalamic–pituitary unit resulted in a better understanding of the regulatory principles, and may provide a basis for a more physiological approach to LH-RH therapy of hypothalamic ovarian failure.

It is now generally accepted that, on the basis of LH-RH measurements in pituitary stalk effluent of the rhesus monkey (Carmel et al., 1976) and on the basis of pulsatile LH serum levels in the rhesus monkey (Dierschke et al., 1970) and in the human (Yen et al., 1972), the hypothalamic LH-RH secretion is pulsatile in character, with a rather circhoral (Knobil, 1974) frequency. During the follicular phase of the human menstrual cycle, hypothalamic LH-RH pulses seem to occur every 90 min.

In the rhesus monkey with hypothalamic lesions and abolished gonadotropic hormone release from the pituitary gland only intermittent (one pulse per hour) administration of synthetic LH-RH re-established pituitary gonadotropin secretion, while initiation of continuous administration of LH-RH resulted in a breakdown of the re-established gonadotropic function (Belchetz et al., 1978).

Each pulse of LH-RH not only induces the release but also the new synthesis of gonadotropins, which is accomplished approximately 1 h following the LH-RH stimulus. This is indicated by LH-RH double-stimulation tests, which could demonstrate 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 time lapse of 60–120 min (Römmler, 1978).

These findings were further substantiated by ultrastructural studies of rat pituitary gonadotropes, demonstrating that parallel to the LH-RH-induced extrusion of LH secretory granules new secretory granules appeared with a maximum number of granules 1–2 h following the administration of LH-RH. In addition to release and synthesis of LH, also processes of degradation of LH-containing granules were initiated by the administration of LH-RH (Römmler et al., 1978).

These findings indicate that the pituitary gonadotropes are subjected to LH-RH-induced circhoral functional cycles, consisting of intimately correlated processes (release, synthesis, storage and degradation of gonadotropins), and which are probably in a differential manner further modulated by the pituitary effects of gonadal steroids. In addition, cyclicity of hypothalamic stimulation of the pituitary gland results in a functional synchronization of all or at least a great proportion of the gonadotropes, rendering the hypothalamic–pituitary unit a very economic system.

In view of these considerations and findings, circhoral pulsatile release of hypothalamic LH-RH constitutes a prerequisite of normal pituitary function. This may also explain why the long-term administration of long-acting LH-RH analogues does not result in an improvement but rather in a deterioration of pituitary gonadotropic function (Dericks-Tan et al., 1977; Hanker et al., 1978).

The results of Nakai et al. (1978), who were able to demonstrate that in the ovariectomized, hypothalamus-lesioned rhesus monkey pulsatile substitution of LH-RH with a circhoral pattern of administration resulted in a restoration of previously abolished pituitary gonadotropic function, prompted similar studies in the severe hypothalamic amenorrhea (Leyendecker, in preparation).

In a 25-yr-old primary amenorrheic woman, a test dose of 100 μg of LH-RH i.v. did not result in a pituitary response (Fig. 5a). During treatment with 10 μg LH-RH i.v. every 90 min over a period of 17 days, a slow increase of FSH and LH serum levels was observed. Previously undetectable levels of estradiol in serum now rapidly increased to levels of the mid-follicular phase (Fig. 5b). On day 10, a selective breakdown of pituitary FSH function occurred, while LH levels remained unaffected. Sections of days 10 and 17 with a more frequent blood sampling show that the previously unresponsive pituitary is now functioning normally with respect to the LH-RH-induced pulsatile serum pattern of LH (Fig. 5c and d).

In a 22-yr-old woman with progestogen-negative secondary amenorrhea the same regimen was applied (Fig. 6a–d). Following a test dose of 100 μg of LH-RH i.v., a slight pituitary response was observed. During treatment with LH-RH (10 μg i.v. every 90 min) estradiol serum levels steadily increased, indicating an improvement of pituitary gonadotropic

function. A section of day 10 of the treatment demonstrates a complete imitation of normal gonadotropin pattern in serum. On day 10, as in the former patient, a selective impairment of pituitary FSH function occurred, indicated by a step-like decrease of serum FSH on a lower level. In spite of this selective decrease of serum FSH, estradiol further increased, and on days 16–19 a pituitary discharge of LH and, to a lesser extent, of FSH occurred. The section on day 19 demonstrates the pulsatile pattern of serum LH during the descending limb of this 'mid-cycle peak'. The selective impairment of pituitary FSH function starting on day 10 in both women is interpreted as being the result of a selective ovarian negative feedback inhibition on FSH.

A comparison of the serum levels of FSH, LH and estradiol of these two patients prior to and during LH-RH administration with the respective hormonal levels in the various forms of hypothalamic ovarian failure (Fig. 4) suggests that during recovery under LH-RH treatment the pituitary–ovarian axis in these two women is functionally passing through the different stages of hypothalamic ovarian failure, giving indirect support to the proposed pathophysiological concept.

These preliminary results support the pathophysiological concept of hypothalamic ovarian failure as being the result of a deficient hypothalamic LH-RH secretion. They support findings of Belchetz et al. (1978) in the rhesus monkey that, with pulsatile LH-RH substitution, a long-term re-establishment of pituitary gonadotropic function is possible. Furthermore, they support the concept of hypothalamic LH-RH secretion being only permissive in the primate, with the cyclicity of endocrine events being regulated on pituitary and ovarian levels (Nakai et al., 1978).

Of course, the requirement of pulsatility in the long-term substitution with LH-RH impedes its clinical application. Perhaps an improved technology of application will help to overcome these difficulties.

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